EXHIBIT 13

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF TALC

(CAS NO. 14807-96-6)

IN F344/N RATS AND B6C3F$_1$ MICE

(INHALATION STUDIES)

Scheduled Peer Review Date: June 23-24, 1992

NOTICE

This is a DRAFT Technical Report prepared for public review and comment. Until this DRAFT has been reviewed and approved by the NTP Board of Scientific Counselors' Technical Reports Review Subcommittee in public session, the interpretations described herein do not represent the official scientific position of the National Toxicology Program. Following peer review, readers should contact NTP for the final version of this Technical Report.

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ABSTRACT

TALC
(Non-Asbestiform)

CAS No. 14807-96-6

Molecular Formula: $Mg_3Si_4O_{10}(OH)_2$ Molecular Weight: 379.26

Synonyms: Talcum; Agalite; Emtal 596; non-asbestiform talc; non-fibrous talc; Steatite; hydrous magnesium silicate.

Talc ore may contain several other minerals including calcite, dolomite, magnesite, tremolite, anthophyllite, antigorite, quartz, pyrophyllite, micas, or chlorites. Since talc products are sold in a multitude of grades which have physical or functional characteristics especially suited for particular applications, occupational and consumer exposures to talc are complex. Recently, epidemiology studies have revealed an association between non-fibrous talc and lung cancer risk. Talc was nominated by NIOSH for study by the NTP because of widespread human exposure and because of the lack of adequate information on its chronic toxicity and potential carcinogenicity. Toxicology and carcinogenicity studies of talc (non-asbestiform, cosmetic grade), a finely powdered hydrous magnesium silicate, were conducted by exposing groups of F344/N rats to aerosols for 6 hours daily, 5 days per week for up to 113 weeks for males and 122 weeks for females. Groups of $B6C3F_1$ mice were exposed similarly for up to 103 or 104 weeks.

Lifetime Study in Rats

Groups of 50 male and 49 or 50 female rats were exposed to aerosols containing 0, 6, or 18 mg/m³ talc until mortality in any exposure group reached 80% (113 weeks for males and 122 weeks for females). In a special study, additional groups of 22 male and 22 female rats were similarly exposed and examined for interim pathology evaluations or pulmonary function tests after 6, 11, 18, and 24 months and lung biochemistry and cytology studies after 24 months. The talc aerosols had a median mass aerodynamic diameter of 2.7 μm in the 6 mg/m³ chamber and a median diameter of 3.2 μm in the 18 mg/m³ chamber with geometric standard deviations of 1.9 μm. However, there was a 7-week period beginning at study week 11 during which the chamber concentration for the 18 mg/m³ rats varied from approximately 30 to 40 mg/m³ because of difficulties with the aerosol concentration monitoring system. Further, there was a 12-week period beginning at approximately week 70 during which there were difficulties in generating the talc aerosol, and the chamber concentrations for rats and mice were substantially lower than the target concentrations.

Survival, Body Weights, and Clinical Findings

The survival of male and female rats exposed to talc was similar to that of the controls. Mean body weights of rats exposed to 18 mg/m³ were slightly lower than those of controls after week 65. No clinical findings were attributed to talc exposure.

Pathology Findings

Absolute and relative lung weights of male rats exposed to 18 mg/m³ were significantly greater than those of controls at the 6-, 11-, and 18-month interim evaluations and at the end of the lifetime study, while those of female rats exposed to 18 mg/m³ were significantly greater at the 11-, 18-, and 24-month interim evaluations and at the end of the lifetime study. Inhalation exposure of rats to talc produced a spectrum of inflammatory, reparative, and proliferative processes in the lungs. Granulomatous inflammation occurred in nearly all exposed rats and the severity increased with exposure duration and concentration. Hyperplasia of the alveolar epithelium and interstitial fibrosis occurred in or near foci of inflammation in many exposed rats, while squamous metaplasia of the alveolar epithelium and squamous cysts were also occasionally seen. Accumulations of macrophages (histiocytes), most containing talc particles, were found in the peribronchial lymphoid tissue of the lung and in the bronchial and mediastinal lymph nodes. In female rats, the incidences of alveolar/bronchiolar

adenoma, carcinoma, and adenoma or carcinoma (combined) in the 18 mg/m^3 group were significantly greater than those of controls. The incidences of pulmonary neoplasms in exposed groups of male rats were similar to those in controls.

Minor alterations attributed to talc exposure were also seen in the upper respiratory tract. Hyperplasia of the respiratory epithelium of the nasal mucosa in males and accumulation of cytoplasmic, eosinophilic droplets in the nasal mucosal epithelium in male and female rats occurred with a concentration-related increased incidence in the exposed groups.

Adrenal medulla pheochromocytomas (benign, malignant, or complex combined) occurred with a significant positive trend in male and female rats, and the incidences in the 18 mg/m^3 groups were significantly greater than those of controls. Although adrenal medulla hyperplasia occurred with similar frequency among exposed and control females, the incidences of hyperplasia in exposed males were significantly lower than in controls.

Lung Talc Burden

Lung talc burdens of male and female rats exposed to 6 mg/m^3 were similar and increased progressively from 6 to 24 months. Lung talc burdens of females exposed to 18 mg/m^3 also increased progressively from 6 to 24 months, while those of males exposed to 18 mg/m^3 remained about the same after 18 months. Lung burdens were generally proportional to exposure concentration at each interim evaluation.

Pulmonary Function, Bronchoalveolar Lavage, and Lung Biochemistry

In exposed male and female rats there was a concentration-related impairment of respiratory function which increased in severity with increasing exposure duration. The impairment was characterized by reductions in lung volume (total lung capacity, vital capacity, and forced vital capacity), lung compliance, gas exchange efficiency (carbon monoxide diffusing capacity), and nonuniform intrapulmonary gas distribution.

After 24 months, rats exposed to talc had significant increases in total protein, ß-glucuronidase, lactate dehydrogenase, alkaline phosphatase, and polymorphonuclear leukocytes in bronchoalveolar lavage fluid. Viability and phagocytic activity of macrophages recovered from lavage fluid were not affected by talc exposure.

Total lung collagen was significantly increased in rats at both exposure concentrations after 24 months, while collagenous peptides in lavage fluid and percent newly synthesized protein from females, but not males, were also significantly increased at the 6 or 18 mg/m^3 levels. In addition, lung proteinase activity, primarily cathepsin D-like activity, was significantly greater in exposed males and females. Rats exposed to talc also had significant increases in collagenous peptides and acid proteinase in lung homogenates.

2-Year Study in Mice

Groups of 47 to 49 male and 48 to 50 female mice were exposed to aerosols containing 0, 6, or 18 mg/m^3 talc for up to 103 or 104 weeks. In a special study, additional groups of 39 or 40 male and 40 female mice similarly exposed were examined for interim pathology evaluations, lung biochemistry, and cytology studies after 6, 12, and 18 months of exposure. The talc aerosols had a median mass aerodynamic diameter of 3.3 μm with a geometric standard deviation of 1.9 μm in the 6 mg/m^3 chamber, and a median diameter of 3.6 μm with a geometric standard deviation of 2.0 μm in the 18 mg/m^3 chamber.

Survival, Body Weights, and Clinical Findings

Final mean body weights and survival of male and female mice exposed to talc were similar to those of the controls. There were no clinical findings attributed to talc exposure.

Pathology Findings

Inhalation exposure of mice to talc was associated with chronic active inflammation and the accumulation of macrophages in the lung. In contrast to rats, hyperplasia of the alveolar epithelium, squamous metaplasia, or interstitial fibrosis were not associated with the inflammatory response in mice, and the incidences of pulmonary neoplasms in exposed and control groups of mice were similar. Accumulations of macrophages (histiocytes) containing talc particles were also present in the bronchial lymph node.

In the upper respiratory tract, cytoplasmic alteration, consisting of the accumulation of cytoplasmic eosinophilic droplets in the nasal mucosal epithelium, occurred with a concentration-related increased incidence in exposed male and female mice.

Lung Talc Burden

Lung talc burdens of mice exposed to 6 mg/m³ were similar between males and females and increased progressively from 6 to 24 months, except for males at 18 months. The lung talc burdens of mice exposed to 18 mg/m³ were also similar between the sexes at each interim evaluation. Although the talc burdens of males and females increased substantially from 6 to 24 months, the values at 12 and 18 months were similar. Generally, lung burdens of mice exposed to 18 mg/m³ were disproportionately greater than those of mice exposed to 6 mg/m³, suggesting that clearance of talc from the lung was impaired, or impaired to a greater extent, in mice exposed to 18 mg/m³ than in mice exposed to 6 mg/m³.

Bronchoalveolar Lavage and Lung Biochemistry

Increases in total protein, ß-glucuronidase, lactate dehydrogenase, and glutathione reductase, total nucleated cells, and polymorphonuclear leukocytes in bronchoalveolar lavage fluid were observed primarily in mice exposed to 18 mg/m³, although some parameters were also increased in mice exposed to 6 mg/m³.

The amount of collagenous peptides in lavage fluid and total lung collagen were increased in male and female mice exposed to 18 mg/m³. Acid proteinase activity, principally cathepsin D-like activity, of lung homogenate supernatant fluid was also significantly increased in mice at the 18 mg/m³ exposure concentration.

CONCLUSIONS

Under the conditions of these inhalation studies, there was *some evidence of carcinogenic activity** of talc in male F344/N rats based on an increased incidence of benign and malignant pheochromocytomas of the adrenal gland. There was *clear evidence of carcinogenic activity* of talc in female F344/N rats based on increased incidences of alveolar/bronchiolar adenomas and carcinomas of the lung and benign and malignant pheochromocytomas of the adrenal gland. There was *no evidence of carcinogenic activity* of talc in male or female $B6C3F_1$ mice exposed to 6 or 18 mg/m³.

The principal toxic lesions associated with inhalation exposure to talc in rats included chronic granulomatous inflammation, alveolar epithelial hyperplasia, squamous metaplasia and squamous cysts, and interstitial fibrosis of the lung. These lesions were accompanied by impaired pulmonary function characterized primarily by reduced lung volumes, reduced dynamic and/or quasistatic lung compliance, reduced gas exchange efficiency, and nonuniform intrapulmonary gas distribution. In mice, inhalation exposure to talc produced chronic inflammation of the lung with the accumulation of alveolar macrophages.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9.

Summary of the Lifetime and 2-Year Carcinogenicity Studies of Talc

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Exposure levels	0, 6, or 18 mg/m^3	0, 6, or 18 mg/m^3	0, 6, or 18 mg/m^3	0, 6, or 18 mg/m^3
Body weights	High-dose group slightly lower than controls	High-dose group slightly lower than controls	Exposed groups similar to controls	Exposed groups similar to controls
Survival rates	9/50, 14/50, 16/50	11/50, 13/49, 9/50	30/47, 28/48, 32/49	30/49, 23/48, 25/50
Neoplastic effects	Adrenal medulla: benign or malignant pheochromocytoma (26/49, 32/48, 37/47)	Lung: alveolar/bronchiolar adenoma (1/50, 0/48, 9/50); alveolar/bronchiolar carcinoma (0/50, 0/48, 5/50); alveolar/bronchiolar adenoma or carcinoma (1/50, 0/48, 13/50) Adrenal medulla: benign or malignant pheochromocytoma (13/48, 14/47, 23/49)	None	None
Nonneoplastic effects	Lung: granulomatous inflammation (2/49, 50/50, 49/50); interstitial fibrosis (1/49, 16/50, 33/50); alveolar epithelial hyperplasia (5/49, 26/50, 38/50); peribronchial hyperplasia (0/49, 12/50, 8/50); cyst (0/49, 0/50, 3/50); alveolar squamous metaplasia (0/49, 0/50, 2/50) Lymph node (bronchial): histiocytic hyperplasia (0/41, 44/48, 46/49); (mediastinal) histiocytic hyperplasia (0/48, 40/49, 43/47) Nose: respiratory epithelial hyperplasia (0/49, 3/48, 14/47); cytoplasmic alteration (3/49, 18/48, 40/47)	Lung: granulomatous inflammation (2/50, 47/48, 50/50); interstitial fibrosis (1/50, 24/48, 44/50); alveolar epithelial hyperplasia (2/50, 27/48, 47/50); peribronchial hyperplasia (0/50, 8/48, 9/50); cyst (0/50, 1/48, 7/50); alveolar squamous metaplasia (0/50, 0/48, 8/50) Lymph node (bronchial): histiocytic hyperplasia (0/46, 40/47, 45/47); (mediastinal) histiocytic hyperplasia (0/47, 33/44, 40/47) Nose: cytoplasmic alteration (5/48, 23/45, 46/48)	Lung: chronic inflammation (0/45, 16/47, 40/48); macrophage hyperplasia (3/45, 46/47, 48/48) Lymph node (bronchial): histiocytic hyperplasia (1/32, 32/39, 42/44) Nose: cytoplasmic alteration (5/45, 23/46, 40/47)	Lung: chronic inflammation (0/46, 25/48, 38/50); macrophage hyperplasia (2/46, 45/48, 43/50) Lymph node (bronchial): histiocytic hyperplasia (0/38, 25/37, 39/43) Nose: cytoplasmic alteration (29/46, 37/46, 40/50)
Level of evidence of carcinogenic activity	Some evidence	Clear evidence	No evidence	No evidence

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS

TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on talc on June 23-24, 1992, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

NOTE: A summary of the Technical Reports Review Subcommittee's remarks will appear in a future draft of this report.

INTRODUCTION

TALC
(Non-Asbestiform)

CAS No. 14807-96-6

Molecular Formula: $Mg_3Si_4O_{10}(OH)_2$ Molecular Weight: 379.26

Synonyms: Talcum; Agalite; Emtal 596; non-asbestiform talc; non-fibrous talc; Steatite; hydrous magnesium silicate

CHEMICAL AND PHYSICAL PROPERTIES

Talc is a fine powder, white to grayish white in color, with a greasy feel and luster. It is insoluble in water, cold acids, and alkalies (*Merck Index*, 1983), has a density of 2.7 to 2.8, and a melting point of 900° to 1,000° C (Hawley, 1977). Talc as a pure mineral is composed of 63.5% SiO_2, 31.7% MgO, and 4.8% H_2O (Pooley and Rowlands, 1977).

PRODUCTION, USE, AND HUMAN EXPOSURE

Talc is produced by open pit or underground mining of talc rocks and processed by crushing, drying, and milling. Contaminating minerals including iron, nickel, manganese, chromium, aluminum, and titanium are separated from talc by flotation or elutriation. Talc is then finely powdered, treated with boiling diluted hydrochloric acid, washed well, and dried (Osol, 1980). Geological formation of talc rock results from the alteration of magnesia- and silica-rich ultramafic rocks under a range of temperatures and pressures. These hydrothermal alterations may lead to the formation of other mineral phases such as tremolite and serpentine minerals, including chrysotile. These mineral phases may occur as microscopic intergrowths, nodules, or discrete zones within or adjacent to talc (Rohl *et al.*, 1976).

United States production of talc for 1985 was estimated at 1.1 million metric tons, with industrial pattern of use as follows: ceramics, 37%; paints, 19%; paper, 10%; roofing, 10%; plastics, 7%, cosmetics, 5%; rubber, 3%; insecticides, 1%; and other uses, 9% (Bureau of Mines, 1986). Commercial talc is categorized into cosmetic grade, which is free of asbestos, and industrial grade, which contains other minerals including asbestos (Hildick-Smith, 1976).

A comprehensive review of the literature before 1987 on the use, exposure, and biological effects of talc was published by IARC (1987). Talc is used as a dusting powder, including baby powder, either alone or with starch or boric acid, for medicinal or toiletry preparations; as an excipient and filler for pills and tablets; and for dusting tablet molds (*Merck Index*, 1983). It is also used as a filler and pigment for paints, putty, and plaster; as a carrier and diluent for pesticides; as an additive to clay in ceramic manufacture; in paper coatings; and for the manufacture of rubber and roofing materials (Hawley, 1977). The recommended time-weighted average (TWA) human exposure level for talc containing no asbestos fibers is 2 mg/m^3 (ACGIH, 1989).

A large segment of the population is potentially exposed to talc. The number of workers exposed to talc was estimated at 1,371,201, which includes 349,228 females (NIOSH, 1990). In addition, the public is potentially exposed to talc through its many uses in pharmaceuticals and consumer products. Based on its uses, human exposure to talc can occur via inhalation, ingestion, or dermal exposure.

ABSORPTION, DISTRIBUTION, AND EXCRETION

Experimental Animals

The absorption and disposition of ^{3}H-labeled talc in rats, mice, and guinea pigs administered a single oral dose, as well as its translocation in rabbits administered a single or multiple intravaginal dose was studied by Phillips *et al.* (1978). The oral doses

were 50 mg/kg for rats, 40 mg/kg for mice, and 25 mg/kg for guinea pigs. Rabbits were given either a single intravaginal dose of 50 mg/kg or the same dose once a day for 6 days. In rats, mice, and guinea pigs, more than 95% of the dose was excreted in the feces 3 to 4 days after dosing. Less than 2% of the radioactivity was recovered in the urine. This radioactivity probably reflected contamination of urine samples with feces. No radioactivity was found in the liver or kidneys of these animals. No translocation of talc was found in the ovaries of rabbits.

Hanson *et al.* (1985) and Pickrell *et al.* (1989) studied the lung burden in groups of 5 male and 5 female F344/N rats and B6C3F$_1$ mice following inhalation exposure to concentrations of talc for 6 hours daily, 5 days per week, for 4 weeks. The mean exposure concentrations used were 2.3, 4.3, or 17 mg/m^3 for rats and 2.2, 5.7, or 20.6 mg/m^3 for mice. The resulting lung talc burdens were 0.08, 0.19, and 0.87 mg/g of lung for rats and 0.1, 0.33, and 1.2 mg/g of lung for mice. These data clearly indicate that the amount of talc retained per unit of lung tissue was proportional to the exposure concentration of talc.

Pulmonary deposition, translocation, and clearance of neutron-activated talc was studied in hamsters after a single, 2-hour, nose-only inhalation exposure (Wehner *et al.*, 1977a,b). Deposition of talc in the lung was demonstrated by X-ray fluorescence and X-ray diffraction. An estimated 6% to 8% of the inhaled quantity was deposited in the alveoli. The biological half-life of the talc deposited in the alveoli was estimated at 7 to 10 days. No translocation of talc to liver, kidneys, ovaries, or other parts of the body was found.

Humans

Talc, a filler in some drugs injected by addicts, was found in the lung (Groth *et al.*, 1972; Lamb and Roberts, 1972; Farber *et al.*, 1981; Crouch and Churg, 1983), spleen, kidney, liver, brain, adrenal gland, thyroid gland (Groth *et al.*, 1972), and retina (Atlee, 1972) of some addicts. In the lung, most of the talc particles were seen within the vessels of the alveolar walls and were often associated with marked foreign body granulomas (Crouch and Churg, 1983).

TOXICITY

Experimental Animals

The LD$_{50}$ for talc has not been established. Talc caused death in guinea pigs given 2 or 3 injections of 25 mg talc in saline (Dogra *et al.*, 1977) and in rats receiving a splenic injection of 1,400 mg/kg body weight (Eger and DaCanalis, 1964). Deaths occurred in rats exposed to a very dense atmosphere of talc (particle size <5 μm) 3 hours a day, for 12 days (Policard, 1940). The concentration of talc in the atmosphere was not known and the observed mortality may have been due to suffocation.

Wagner *et al.* (1977) reported on the toxic effects of talc in rats exposed orally or by inhalation. No significant decrease in mean life span and no pathologic effects were found in rats fed 100 mg talc for 101 days. Rats exposed to talc atmospheres of 10.8 mg/m^3 (particle size, 25 mm) for 3 months showed minimal lung fibrosis, and no change in severity occurred during the postexposure period. By contrast, rats exposed to the same atmospheres for 1 year showed minimal to slight fibrosis, and the severity had increased to moderate within a year after cessation of exposure. Rats exposed to atmospheres of 30 to 383 mg/m^3 "industrial" or "pharmaceutical" talc for 9 months developed chronic inflammatory changes, including thickening of the pulmonary artery walls and emphysema (Bethege-Iwanska, 1971). Hamsters exposed to respirable aerosols containing 8 mg/m^3 of cosmetic grade talc for 150 minutes a day, 5 days per week, for 300 days showed no histopathologic changes in the lung, heart, liver, renal tissue, or uterus (Wehner, 1980).

Rats given a single intratracheal injection of 50 mg of pure talc in water did not show lung fibrosis or lymph node abnormalities. Those given the same dose of "calcined" talc developed lung and lymph node fibrosis (Luchtrath and Schmidt, 1959). These differing results may be related to differences in the crystal structures of "pure" and "calcined" talc. Bronchiolar inflammation occurred in rats 4 days after an intratracheal injection of 25 mg of talc (containing tremolite) in water; collagenous tissue developed within a few months after injection (Gross *et al.*, 1970).

Injection of 10 mg of talc containing some asbestos into the pleural cavity of mice produced granulomas (Davis, 1972). A single injection of 20 mg of talc into the right pleural cavity of rats produced granulomas at the injection site; one lung adenoma was also observed but no other changes related to talc administration were observed in the lung (Wagner *et al.*, 1977). Rats with abdominal muscle implants of suture materials dusted with talc or talc pellets initially showed mild to moderate acute inflammation, followed by chronic inflammation and granuloma formation within 3 days (Sheikh *et al.*, 1984).

Rats with subcutaneous inflammation caused by talc had a decrease in bone formation as evidenced by hypozincemia and a decrease in metaphyseal trabecular surfaces. Both hypozincemia and the decrease in osteoblast trabecular surfaces were directly proportional to the number of granulomas present (Marusic *et al.*, 1990).

Talc produced retinopathy in adult Rhesus monkeys given intravenous injections of talc once every 2 weeks for 3.5 to 10 months. Talc particles were found lodged in the precapillary arterioles and capillaries, producing a focal occlusion of retinal and choroidal capillaries (Kaga *et al.*, 1982a,b).

Humans

Exposure to industrial grade talc dust causes pulmonary fibrosis, however, reports on cosmetic grade talc dust are conflicting. Hildick-Smith (1976) reported that cosmetic grade talc did not appear to be injurious to health, while Vallyathan and Craighead (1981) reported that it was. Four of seven workers exposed to heavy concentrations (0.4 to 36 mg/m^3) of cosmetic grade talc for 4 to 27 years had histologic evidence of pulmonary fibrosis at death (Thariault *et al.*, 1974). Wells *et al.* (1979) also noted chronic pulmonary degenerative disease in a housewife who reported heavy use of cosmetic talc. Inhalation of pure talc is known to result in a disease known as talcosis, which may include acute or chronic bronchitis and interstitial inflammation. Radiographically, the lesion appears as a small, irregular nodule, typical of a small-airway obstruction. Intravenous administration of talc-containing oral medications by abusers causes vascular granulomas (Feigin, 1986). Intravenous talcosis was diagnosed in a 36-year-old woman who was a drug abuser (Hill *et al.*, 1990). Talcosis in this patient was identified by the presence of peripheral nodular lesions on chest X-rays and was confirmed by the presence of birefringent particles in a transbronchial biopsy. Pulmonary talc granulomatosis was diagnosed in a cocaine sniffer (Oubeid *et al.*, 1990). Chest X-rays of a heroin addict who later died of respiratory failure showed a progressive massive fibrosis of the lung secondary to intravenous injection of the drug (Crouch and Churg, 1983). Microscopic examination of lung lesions revealed an active granulomatous reaction with associated vascular obliteration. Throughout the lesion, refractile birefringent plates of particulate material were noted. Interstitial perivascular and vascular granulomas were noted in the periphery of the lung. The particulate material was identified as talc by X-ray spectroscopy and diffraction methods. Intravenous injection of talc-containing drugs intended for oral use was the cause of pulmonary granulomatosis and pulmonary hypertension in 19 patients (Arnett *et al.*, 1976). In patients with pulmonary hypertension, talc granuloma was found in the pulmonary arteries. In patients without hypertension, talc granuloma was found in the pulmonary interstitium. Patients suffering from talc granulomatosis (confirmed by lung biopsy) as a result of intravenous injection of crushed tablets of pentazocine, had dyspnea, increased angiotensin-converting enzyme concentrations, and increased lymphocytes by bronchoalveolar lavage (Farber *et al.*, 1982). Pneumoconiosis (talcosilicosis) was diagnosed in a 54-year-old female confectionery worker who was exposed to talc dust for 5 years (Canessa *et al.*, 1990). Talc, given by intrapleural instillation to promote pleural symphysis in the palliation of recurrent malignant pleural effusions, caused adult respiratory distress syndrome (ARDS) in three patients (Rinaldo *et al.*, 1983). Symptoms of ARDS included fever, dyspnea, and respiratory failure. ARDS occurred in a 16-month-old baby inhaling baby powder. Normal pulmonary function returned in this patient after 6 years, as determined by a follow-up study (Reyes and Brown, 1989).

CARCINOGENICITY

Experimental Animals

Results of carcinogenicity studies of talc in animals were reviewed by the IARC (1987). The following is an excerpt of this review:

No significant difference in tumor incidence was observed between two groups of Wistar rats (25 animals/sex/group, 10 weeks old) given an equivalent of 50 mg/kg per day of commercial talc (composition not specified) in the diet or the basal diet for life (Gibel *et al.*, 1976). Similar results were obtained in groups of 16 male and 16 female

Wistar rats (21 to 26 weeks old) given 100 mg of Italian talc (particle size, 25 mm; containing 92% talc, 3% chlorite, 1% carbonate minerals, and 0.5 to 1% quartz) per rat per day in the diet or the basal diet for 5 months and observed for life (Wagner *et al.*, 1977). In both studies small numbers of animals were used.

Groups of 24 male and female Wistar rats, 6 to 8 weeks of age, were exposed by inhalation to 10.8 mg/m^3 Italian talc aerosol 7.5 hours a day, 5 days per week, for 6 or 12 months. Ten days after the end of each exposure period, 6 rats in each group were killed; an additional 4 rats were killed one year later. Within 28 months from the beginning of the study, 12 animals in each group had died. No lung tumors were observed in rats exposed to talc for 6 months; one lung adenoma occurred among rats exposed for 12 months. No lung tumors were found in the control rats (Wagner *et al.*, 1977). The adequacy of this study is in question because only a small number of rats survived longer than 12 months.

Three groups of 50 male and female hamsters, 4 weeks of age were exposed to talc aerosol (37.1 mg/m^3, mean respirable fraction 9.8 mg/m^3) for 3, 30, or 150 minutes per day, 5 days a week, for 30 days. Two additional groups of hamsters were exposed to talc aerosol (27.4 mg/m^3, mean respirable fraction 8.11 mg/m^3) for 30 or 150 minutes per day, for 300 days. Two groups of 25 male and female hamsters were exposed to air and served as controls. No primary tumors were found in the respiratory system of any hamster. Twenty-five percent of the hamsters exposed to the aerosols for 30 or 150 minutes for 300 days had alveolar cell hyperplasia compared to 10% in the controls (Wehner *et al.*, 1977a, 1979). The exposure duration of this study was short and considered inadequate.

No local tumors were found in 50 female R3 mice, 3 to 6 months of age, given a 0.2 mL subcutaneous injection of talc of unspecified composition (80 mg talc in peanut oil) and observed for life (Neukomm and de Trey, 1961).

Forty Swiss albino rats, 6 weeks of age and sex unspecified, received a single intraperitoneal injection of 20 mg commercial talc (unspecified composition) in saline. Sixteen animals died by the end of 6 months. Of the 24 mice that lived to termination (time not specified) three had peritoneal mesotheliomas compared to 3 of 46 of the controls (Ozesmi *et al.*, 1985). This study was considered inadequate because of poor reporting.

Forty female Wistar rats, 8 to 12 weeks of age, were given four intraperitoneal injections of 25 mg granular talc in 2 mL saline at weekly intervals. Similarly, 80 females were injected with saline and served as controls. The rats were observed until termination or death (average survival time, 602 days). A mesothelioma occurred in 1 of 36 rats given talc but none was found in the controls (Pott *et al.*, 1974, 1976a,b).

No mesothelioma was observed in two groups of 24 male and female Wistar rats given a single intrapleural injection of 20 mg Italian talc in saline or saline alone. A pulmonary adenoma occurred in one rat that died at 25 months. Mean survival time (655 days for the talc group versus 691 for the controls) was not affected (Wagner *et al.*, 1977).

Groups of 30 to 50 female Osborne-Mendel rats, 12 to 20 weeks of age, received intrapleural implantation of one of seven grades of refined commercial talc from separate sources in hardened gelatin. Rats were observed for up to 2 years at which time survivors were killed. Pleural sarcoma incidences were: grade 1, 1/26; grade 2, 1/30; grade 3, 1/29; grade 4, 1/29; grade 5, 0/30; grade 6, 0/30; grade 7, 0/29. The incidence of pleural sarcoma was 3 of 491 in untreated controls, 17 of 615 in controls receiving implants of "nonfibrous" material described by the authors as "noncarcinogenic," and 14 of 29 in rats receiving UICC crocidolite asbestos (Stanton *et al.*, 1981).

The IARC Working Group noted that in most of the talc studies, no or limited characterization of the mineralogy, fiber content, or particle size of the samples was given. Thus, the group concluded that there was inadequate evidence on the carcinogenicity of talc to experimental animals.

Humans

An epidemiological study of pottery workers in the United States revealed an association between exposure to non-fibrous talc and increased mortality and lung cancer incidence (Thomas and Stewart, 1987). Increased incidences of lung cancer occurred exclusively among pottery workers employed in the manufacture of plumbing fixtures. A later study of employees in three ceramic plumbing fixture factories showed increased mortality from benign respiratory disease and from lung cancer. The

increased incidence in lung cancer was highest among workers who were simultaneously exposed to silica and talc. The lung cancer mortality risk increased with the number of years of exposure to talc, but showed no pattern by the number of years of exposure to silica. Among men exposed to talc, lung cancer risk decreased with age at first exposure to non-fibrous talc and increased with years since first exposure (Thomas, 1990). Whether or not exposure to silica had a promoting effect on lung cancer is not known. No increased risk for lung cancer or benign respiratory disease was found among miners of non-asbestiform talc or talc millers (Wergeland *et al.*, 1990).

A case-control study showed that women who had perineal exposure to deodorizing powders alone or in combination with other talc-containing powders, had a 2.8 times higher risk of developing borderline ovarian tumors than women who were not perineally exposed to powder (Harlow and Weiss, 1989). In an earlier study, the use of talc as a dusting powder on the perineum or on sanitary napkins by women was associated with an increased risk of epithelial ovarian cancer. Women engaged in both practices had a relatively higher risk of developing this type of cancer (Cramer *et al.*, 1982). No information was presented regarding exposure levels or the content of contaminating minerals of the talc used. In another study, the role of exposure to talcum powder, tobacco, alcohol, and coffee, and the histories of tubal sterilization and hysterectomy on ovarian cancer risk was assessed. The study involved 188 women diagnosed with epithelial ovarian cancer and 539 control women. No association was found between the incidence of epithelial ovarian cancer and increasing frequency or duration of talc use, and patients did not differ from control women in the use of talc on sanitary pads, contraceptive diaphragms, or both. (Whittemore *et al.*, 1988).

Reproductive and Teratogenic Effects

Experimental Animals

Talc produced nonspecific abnormalities in chicken eggs at incidences similar to those caused by thalidomide and sulphadimethoxine (Yang, 1977).

No teratologic effects were observed in hamsters, rats, mice, or rabbits after oral administration of talc. The doses used were 1,600 mg/kg for rats and mice on days 6 through 15 of gestation, 1,200 mg/kg for hamsters on days 6 through 10 of gestation, and 900 mg/kg for rabbits on days 6 through 18 of gestation (Food and Drug Research Laboratories, 1973).

Humans

No information on the reproductive or teratogenic effects of talc in humans has been reported.

Genetic Toxicology

There are no published studies on the genotoxicity of talc. The IARC (1987) review of talc included unpublished results from a 1974 study conducted by Litton Bionetics that showed no mutagenic activity for talc *in vitro* or *in vivo*. Talc did not induce mutations in *Salmonella typhimurium* strains TA1530 or HisG46, or in the yeast, *Saccharomyces cerevisiae*. No chromosomal aberrations were observed in human fibroblasts treated with talc *in vitro*. *In vivo* tests conducted in rats gave negative results for induction of chromosomal aberrations in bone marrow cells and dominant lethal mutations in germinal cells.

Study Rationale

Talc was nominated by NIOSH in 1978 for testing by NTP because of the paucity of adequate information on its carcinogenicity and because of widespread human exposure. The inhalation route was chosen because it is the most common route for human exposure.

MATERIALS AND METHODS

Procurement and Characterization of Talc

Talc (MP 10-52 Grade) was obtained from Walsh and Associates (North Kansas City, MO) in two lots (lot numbers W101882 and B5415). The talc purchased was manufactured by the Minerals, Pigments, and Metals Division of Pfizer, Inc. and is one of their microtalc series of products. Both lots were from Pfizer's Barretts, Montana, mine which is a strip mine located between Barretts and Three Brother, Montana. This mine is the only source for the MP 10-52 grade talc. The grade designation is for high purity talc that has a top particle size of 10 μm and according to the manufacturer contains no tremolite or any asbestiform minerals. Lot W101882 was used from the beginning of the 2-year studies through January 1986. Lot B5415 was used in the 2-year studies from 27 January 1986 to the end of the studies on 31 October 1986. The talc was extensively characterized by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO), and by McCrone Associates (Norcross, GA). The methods and results of these studies are detailed in Appendix H.

The study mineral, a finely powdered white solid, was identified as talc by infrared spectroscopy, elemental analysis, Karl Fischer water analysis, thermogravimetric analyses, spark source mass spectrometry, automated scanning electron probe analyses, X-ray diffraction, polarized light microscopy, and transmission electron microscopy. Both lots were shown to be asbestos free by polarized light microscopy and transmission electron microscopy. Results of automated scanning electron microprobe analysis of lot W101882 indicated that the sample was virtually free of silica (1 particle of silica in 1,466 particles examined). Bulk chemical stability studies were not conducted due to the physical and chemical properties of talc. During the study the compound was stored in tightly sealed plastic bags at 25° C.

Generation and Monitoring of Chamber Concentrations

Talc aerosols were generated in a single fluidized-bed generator (FBG) by injecting compressed air into the bed (Figure H2). The aerosolized talc particles were then mixed with diluting air before being delivered to the exposure chambers (Hazelton 1000 and 2000, Lab Products, Inc.). A second FBG for the control chamber contained only the stainless steel bed material (Figures H3 and H4).

Aerosol concentrations were monitored each day in each chamber by taking three, 2-hour filter samples. Background concentrations of suspended particles were measured each day in the control chamber by taking a 6-hour filter sample. A RAM-S forward light scattering monitor (GCA, Bedford, MA) was used to determine the stability of the aerosol concentrations and the need to adjust the aerosol generation system during the exposure. Determinations were made at the beginning, middle, and end of each filter sampling period. The overall mean concentrations were 5.9 and 16.7 mg/m^3 for the mouse study and 6.1 and 18.6 mg/m^3 for the rat study. While the overall means were very close to target concentrations, there were problems experienced in maintaining control of chamber concentrations. Weekly mean exposure concentrations for the 2-year studies are presented in Figures H5 through H8.

Chamber Atmosphere Characterization

Uniformity of the aerosol concentrations in each chamber was determined at approximately 3-month intervals with the RAM-S. The spatial variation as estimated by the relative standard deviation (RSD) was higher in the mouse study than the rat study with values ranging from 12% to 44% (RSD) for the mice and 2% to 31% (RSD) for the rats. To minimize the variation in talc concentrations, the animal cages were rotated once each week.

The time to reach 90% of the target concentration (T_{90}) was approximately 10 minutes. Therefore, the length of the exposure was defined at 6 hours plus the T_{90} of 10 minutes.

The aerosol size distribution was determined once each month for each chamber using a cascade impactor. The average mass mean aerodynamic diameter (MMAD) and the geometric standard deviation (σ_g) were calculated to be 3.3 ± 1.9 μm and 3.6 ± 2.0 μm for the 6 and 18 mg/m^3 mouse

chambers. The values were 2.7 ± 1.9 μm and 3.2 ± 1.9 μm for the 6 and 18 mg/m^3 rat chambers. The individual values are presented in Tables H1 and H2.

Study Design

Groups of 50 male and 50 female rats and mice were selected for whole body inhalation to talc at target concentrations of 0 (chamber controls), 6, or 18 mg/m^3. Rats were exposed for 6 hours daily, 5 days a week until mortality in any exposure group reached 80% (113 weeks for males and 122 weeks for females). Exposure of rats to talc was extended beyond 2 years based on the report that 80% of pulmonary neoplasms induced in rats by inhalation exposure to diesel exhaust occurred after 2 years (Mauderly *et al.*, 1986). Mice were exposed for 103 or 104 weeks. At the conclusion of the exposures, rats were exposed to filtered air for 10 or 11 days, while mice were exposed to filtered air for 10 to 14 days. All animals were subjected to necropsy and a complete pathology evaluation.

Additional special study groups of 22 male and 22 female rats and 40 male and 40 female mice similarly exposed to 0, 6, or 18 mg/m^3 were designated for interim pathology evaluations; lung talc burden measurements; serial pulmonary function measurements (rats only); and lung biochemistry, cytology, and phagocytosis measurements. Rats were evaluated at 6, 11, 18, and 24 months, while mice were evaluated at 6, 12, and 18 months. Insufficient numbers of rats remained alive at week 103 of exposure for both pulmonary function and/or lung biochemistry/cytology and pathology distribution groups, therefore the remaining rats in these groups were combined. The numbers of rats and mice evaluated for pulmonary function and lung biochemistry, cytology, and phagocytosis and the methods used for each of the parameters are presented in Appendix F for rats and Appendix G for mice.

Source and Specification of Animals

Male and female F344/N rats were obtained from Lovelace Inhalation Toxicology Research Institute (Albuquerque, NM). Male and female B6C3F$_1$ mice were obtained from Frederick Cancer Research Center (Frederick, MD). Rats and mice were held 3 weeks before the studies began. Rats were 6 to 7 weeks old, and mice were 7 weeks old, when the studies began. Animal health was monitored by serologic analyses during the studies under the protocols of the NTP Sentinel Animal Program.

Animal Maintenance

Rats and mice were housed individually throughout the studies. Drinking water was available *ad libitum*. Further details of animal maintenance are given in Table 1.

Clinical Examinations and Pathology

All rats and mice were observed twice daily. Clinical observations and body weights were recorded at the beginning of the studies, weekly for 13 weeks, and monthly thereafter.

A necropsy was performed on all rats in the lifetime core study and all mice in the 2-year core study. Organ weights were recorded for the brain, heart, right kidney, liver, and lungs at the end of the studies. During necropsy, all organs and tissues were examined for grossly visible lesions. A complete histopathologic examination was performed on all animals. Tissues for microscopic examination were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned to a thickness of 5 μm, and stained with hematoxylin and eosin.

Microscopic evaluations were completed by the study laboratory pathologist and the pathology data were entered into the Toxicology Data Management System (TDMS). The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit for accuracy of labeling and animal identification and for thoroughness of tissue trimming. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. A quality assessment pathologist reviewed lung and bronchial and mediastinal lymph nodes in rats and mice and nose in male mice for accuracy and consistency of lesion diagnosis.

The quality assessment report and slides were submitted to the Pathology Working Group (PWG) chair, who reviewed tissues for which there was a disagreement in diagnosis between the laboratory and quality assessment pathologists. All pulmonary neoplasms in female rats and representative histopathology slides of adrenal gland (rats), bronchial lymph node, lung, mediastinal lymph node (rats), and nose, or lesions of general interest were presented by the chair to the PWG for review. The PWG included the quality assessment pathologist as

well as other pathologists experienced in rodent toxicologic pathology who examined these tissues without knowledge of dose group or previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the final diagnosis was changed to reflect the opinion of the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analysis of pathology data, the diagnosed lesions for each tissue type were evaluated separately or combined according to the guidelines of McConnell *et al.* (1986).

Statistical Methods

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the Results section of this report. Animals were censored from the survival analyses at the time they were found dead from other than natural causes or were found to be missing; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table tests to identify dose-related trends. All reported P values for the survival analysis are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions presented in Tables A1, A4, B1, B4, C1, C4, D1, and D4 are given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals with that site examined microscopically. For calculation of statistical significance, the incidences of all nonneoplastic lesions and most neoplasms (Tables A2, B2, C2, and D2) are also given as the ratio of the number of affected animals to the number of animals with the site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., skin, intestine, harderian gland, and mammary gland) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Neoplasm Incidences

The majority of tumors in these studies were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was logistic regression analysis, which assumed that the diagnosed tumors were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, tumor prevalence was modeled as a logistic function of chemical exposure and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if it did not significantly enhance the fit of the model. The dosed and control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). When tumors are incidental, this comparison of the time-specific tumor prevalences also provides a comparison of the time-specific tumor incidences (McKnight and Crowley, 1984).

In addition to logistic regression, alternative methods of statistical analysis were used, and the results of these tests are summarized in the appendixes. These include the life table test (Cox, 1972; Tarone, 1975), appropriate for rapidly lethal tumors, and the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart *et al.*, 1979), procedures based on the overall proportion of tumor-bearing animals.

Tests of significance include pairwise comparisons of each dosed group with controls and a test for an overall dose-response trend. Continuity-corrected tests were used in the analysis of tumor incidence, and reported P values are one sided. The procedures described above also were used to evaluate selected nonneoplastic lesions. For further discussion of these statistical methods, see Haseman (1984).

Analysis on Nonneoplastic Lesion Incidences

Because all nonneoplastic lesions in this study were considered to be incidental to the cause of death or not rapidly lethal, the primary statistical analysis used was a logistic regression analysis in which lesion prevalence was modeled as a logistic function of chemical exposure and time. For lesions detected at the interim evaluation, the Fisher exact test was used, a procedure based on the overall proportion of affected animals.

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between dosed and control groups in the analysis of continuous variables. Organ and body weight data that had

approximately normal distributions were analyzed using the parametric multiple comparison procedures of Williams (1971, 1972) and Dunnett (1955). Lung burden parameters that had skewed distributions were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-response trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-response trend (Dunnett's or Dunn's test).

Quality Assurance Methods

The lifetime and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as study records were submitted to the NTP Archives, they were audited by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and preliminary review draft of this NTP Technical Report were conducted. Audit procedures are presented in the reports, which are on file at the NIEHS. The audit findings were reviewed and assessed by the NTP staff so that all discrepancies had been resolved or were otherwise addressed during the preparation of this Technical Report.

TABLE 1
Experimental Design and Materials and Methods in the Lifetime and 2-Year Inhalation Studies of Talc

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Study Laboratory
Lovelace Inhalation Toxicology Research Institute (Albuquerque, NM)

Strain and Species
Rats: F344/N
Mice: B6C3F$_1$

Animal Source
Rats: Lovelace Inhalation Toxicology Research Institute (Albuquerque, NM)
Mice: Frederick Cancer Research Center (Frederick, MD)

Time Held Before Studies
3 weeks

Average Age When Placed on Studies
6-7 weeks

Date of First Exposure
Rats: 2 July 1984
Mice: 4 June 1984

Duration of Exposure
Rats: 6 hours/day, 5 days/week for 113 weeks (males) and 122 weeks (females)
Mice: 6 hours/day, 5 days/week for 103-104 weeks

Date of Last Exposure
Rats: 29 August 1986 (males) and 31 October 1986 (females)
Mice: 30 May 1986

Average Age When Killed
Rats: 120-121 weeks (males) and 129-130 weeks (females)
Mice: 110-112 weeks

Method of Sacrifice
Injection of T-61 solution for all rats in the lifetime study, all rats designated for pathologic evaluation, and all mice. Halothane anesthesia for all rats designated for biochemical interim evaluations.

Necropsy Dates
Rats: 8-9 September 1986 (males) and 10-11 November 1986 (females)
Mice: 9-13 June 1986 (males) and 2-6 June 1986 (females)

Size of Study Groups
50 males and 50 females

Method of Animal Distribution
Assigned to groups by weight and sex using computer-generated random numbers.

Animals per Cage
1

Method of Animal Identification
Toe clip and ear tag

Diet
NIH-07 Rat and Mouse Ration (Zeigler Bros., Gardner, PA) available *ad libium* during nonexposure periods

Maximum Storage Time for Feed
90 days

TABLE 1
Experimental Design and Materials and Methods in the Lifetime and 2-Year Inhalation Studies of Talc
(continued)

Water
Automatic Watering System (Edstrom), available *ad libitum*

Cages
Stainless steel mesh cages (Hazleton, Aberdeen, MD)

Chambers
Rats: Stainless steel multitiered whole-body exposure chambers (H2000, Hazleton Systems, Aberdeen, MD), washed once weekly
Mice: Stainless steel multitiered whole-body exposure chambers (H1000, Hazleton Systems, Aberdeen, MD), washed once weekly

Bedding
Untreated paper cage board (Shepherd Specialties Paper, Inc., Kalamazoo, MI), changed twice a day

Filters
Room Air and Chamber Air High Efficiency Particulate Air (HEPA) Filter (prefilter and exit filter), MIL Spec MIL-F-51068C (Flanders, Washington, DC)

Animal Room Environment

Rats
Average temperature: 24° C
Relative humidity: 9%-100%
Fluorescent light: 12 hours/day
Room air changes: minimum of 10 changes/hour

Mice
Average temperature: 24° C
Relative humidity: 10%-100%
Fluorescent light: 12 hours/day
Room air changes: minimum of 10 changes/hour

Exposure Concentrations
0, 6, and 18 mg/m^3 by inhalation

Type and Frequency of Observation
Observed twice daily; body weights and clinical findings recorded at study initiation, weekly through week 13, and monthly thereafter

Necropsy
Necropsy performed on all animals. Organ weights recorded for brain, heart, right kidney, liver, and lung.

Histopathology
Complete histopathologic examinations performed on all animals. In addition to tissue masses and gross lesions, tissues examined included: adrenal gland, bone (including marrow), brain, clitoral gland (female rats), epididymis, esophagus, gallbladder (mice), harderian gland (female rats and mice), heart, kidney, large intestine (cecum, colon, rectum), larynx, liver, lung, lymph nodes (bronchial, mandibular, mediastinal, mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland (male rats), prostate gland, salivary gland, seminal vesicle, skin, small intestine (duodenum, ileum, jejunum), spleen, stomach (forestomach, glandular), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus.

RESULTS

RATS

4-WEEK STUDY DOSE SELECTION

Selection of 6 or 18 mg talc/m^3 as the exposure concentrations was based on the results of a 4-week inhalation study in F344/N rats to determine lung talc burden and histopathologic changes associated with talc exposure. These studies indicated that the amount of talc retained in the lung was similar between sexes and proportional to exposure concentration (Appendix K). Microscopic examination of the lungs revealed an accumulation of alveolar macrophages in the lungs only at the 18 mg/m^3 concentration. Based on these findings it was predicted that aerosol concentrations greater than 18 mg/m^3 would overwhelm lung clearance mechanisms, impair lung function, and possibly shorten survival.

LIFETIME STUDY

Survival

Estimates of survival probabilities for male and female rats are shown in Table 2 and in the Kaplan-Meier curves in Figure 1. Survival of exposed male and female rats was similar to that of the controls.

Body Weights and Clinical Findings

The mean body weights of male and female rats exposed to 6 mg/m^3 talc were similar to those of controls throughout the study (Tables 3 and 4, and Figure 2). Mean body weights of male and female rats exposed to 18 mg/m^3 were slightly lower than those of controls, particularly after week 65. The final mean body weight of males in the 18 mg/m^3 group was 4% lower than that of the controls, while the final mean body weight of females in the 18 mg/m^3 group was 14% lower than that of the controls.

Serological tests were performed prior to the beginning of the study and after 6, 12, and 18 months of exposure; serological tests were negative for all microorganisms tested (Table J1). After 24 months and 28 and 30 months (females), the serological tests were positive for Kilham rat virus (KRV), Sendai virus, and rat coronavirus/sialodacryoadenitis virus (RCV/SDA). The significance of the positive KRV titer is unknown since it was found in only one rat and was not observed at later times. No clinical findings or gross or microscopic lesions that could be attributed to Sendai virus or RCV/SDA infections were observed in the talc exposed or control groups. Since there was no clinical or pathological evidence of disease and since the infection occurred very late in the study, these subclinical infections are believed to have had no impact on the study results.

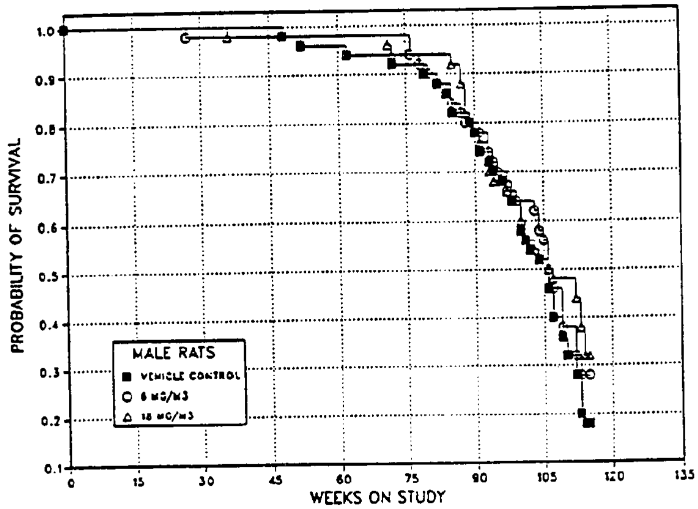
Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplastic or nonneoplastic lesions of the lung, lymph node, nose, and adrenal medulla. Summaries of the incidences of nonneoplastic lesions and neoplasms, the individual animal neoplasm diagnoses, and the statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one group are presented in Appendix A for male rats and Appendix B for female rats.

TABLE 2
Survival of Rats in the Lifetime Inhalation Study of Talc

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
Lifetime Study Groups			
Animals initially in study	50	50	50
Natural deaths	18	17	14
Moribund kills	23	19	20
Animals surviving to study termination	9	14	16
Percent survival at end of study[a]	18	28	32
Mean survival (days)[b]	696	707	711
Survival analysis[c]	P=0.217N	P=0.422N	P=0.192N
Special Study Groups[d]			
Animals initially in study	22	22	22
Natural deaths	2	2	6
Moribund kills	9	5	6
Scheduled sacrifice	11	15	10
Females			
Lifetime Study Groups			
Animals initially in study	50	50	50
Natural deaths	11	19	14
Moribund kills	28	17	27
Missing[d]	0	1	0
Animals surviving to study termination	11	13	9
Percent survival at end of study[a]	22	28	18
Mean survival (days)[b]	743	753	758
Survival analysis[c]	P=0.846	P=0.805N	P=0.977
Special Study Groups[d]			
Animals initially in study	22	22	22
Natural deaths	2	1	2
Moribund kills	5	3	8
Scheduled sacrifice	15	18	12

a Kaplan-Meier determinations
b Mean of all deaths (uncensored, censored, and terminal sacrifice).
c The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the dosed columns. A negative trend or lower mortality in a dose group is indicated by N.
d Censored from survival analyses



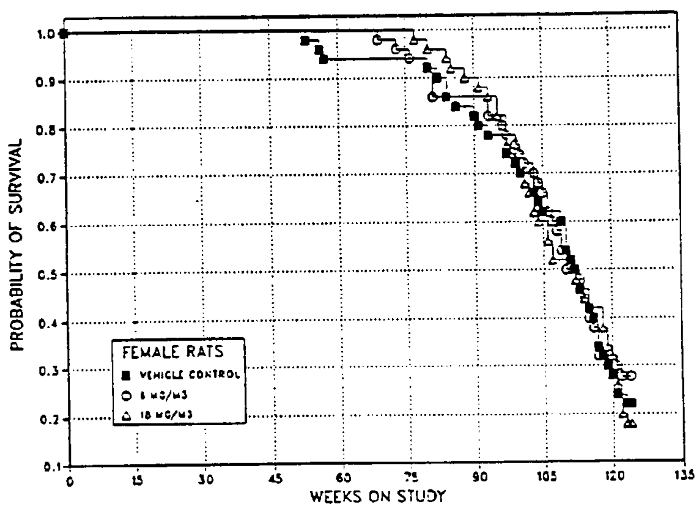


FIGURE 1
Kaplan-Meier Survival Curves for Male and Female Rats Administered Talc by Inhalation for Their Lifetime

TABLE 3
Mean Body Weights and Survival of Male Rats in the Lifetime Inhalation Study of Talc

Weeks on Study	0 mg/m³ Av. Wt. (g)	0 mg/m³ Number of Survivors	6 mg/m³ Av. Wt. (g)	6 mg/m³ Wt. (% of controls)	6 mg/m³ Number of Survivors	18 mg/m³ Av. Wt. (g)	18 mg/m³ Wt. (% of controls)	18 mg/m³ Number of Survivors
1	118	72	121	103	72	119	101	72
2	174	72	174	100	72	174	100	72
3	201	72	200	100	72	202	101	72
4	225	72	215	95	72	219	97	72
5	237	72	239	101	72	238	101	72
6	250	72	252	101	72	251	100	72
7	265	72	263	99	72	263	99	72
8	275	72	270	98	72	269	98	72
9	287	72	280	98	72	281	98	72
10	297	72	293	99	72	293	99	72
11	304	72	300	99	72	297	98	72
13	317	72	315	100	72	312	98	72
17	339	72	338	100	72	331	98	72
21	359	72	355	99	72	351	98	72
25	374	71	370	99	72	367	98	72
29[a]	380	68	378	99	68	369	97	69
33	398	68	393	99	68	386	97	69
38	407	68	405	100	68	393	97	68
41	413	68	412	100	68	401	97	68
45	421	68	420	100	68	410	97	68
49[a]	431	63	428	99	65	418	97	65
53	434	62	432	100	65	422	97	65
57	435	62	432	99	65	424	97	65
61	443	62	442	100	65	430	97	65
65	450	61	444	99	65	432	96	65
69	448	61	440	98	65	429	96	65
73	453	60	442	98	65	432	95	63
77	452	60	441	98	63	429	95	62
81[a]	444	55	434	98	57	423	95	59
85	450	49	434	97	53	424	94	57
89	447	47	437	98	50	424	95	51
93	434	43	429	99	48	408	94	46
97	429	40	427	100	41	407	95	40
101	410	34	395	96	40	394	96	34
105[a]	390	29	391	100	35	385	99	28
109	377	18	390	104	19	376	100	24
113	358	11	389	109	15	342	96	21
Terminal sacrifice		9			14			16
Mean for weeks								
1-13	246		244	99		243	99	
14-52	391		389	99		381	97	
53-113	428		425	99		411	96	

[a] Interim evaluations occurred during weeks 27, 47, 79, and 105.

TABLE 4
Mean Body Weights and Survival of Female Rats in the Lifetime Inhalation Study of Talc

Weeks on Study	0 mg/m³		6 mg/m³			18 mg/m³		
	Av. Wt. (g)	Number of Survivors	Av. Wt. (g)	Wt. (% of controls)	Number of Survivors	Av. Wt. (g)	Wt. (% of controls)	Number of Survivors
1	97	72	101	104	72	98	101	72
2	126	72	127	101	72	125	99	72
3	136	72	139	102	72	138	101	72
4	149	72	144	97	72[a]	145	97	72
5	153	72	159	104	72	154	100	72
6	160	72	165	103	72	160	101	72
7	165	72	169	102	72	166	101	72
8	168	72	171	102	72	168	100	72
9	174	72	176	101	72	173	100	72
10	178	72	182	102	72	179	101	72
11	181	72	184	102	72	181	100	72
13	186	72	191	103	72	187	101	72
17	194	72	201	104	72	197	101	72
21	206	72	211	103	72	207	101	72
25	213	72	216	101	72	214	100	72
29[b]	215	68	219	101	69	213	99	69
33	224	68	227	101	69	221	99	69
38	233	68	237	102	69	229	98	69
41	239	68	242	101	69	235	98	69
45	248	68	251	101	69	242	98	69
49[b]	256	65	259	101	66	252	98	66
53	266	65	270	102	66	260	98	66
57	276	62	277	101	66	269	98	65
61	285	62	288	101	66	276	97	65
65	290	61	288	100	66	277	96	65
69	296	61	292	99	66	281	95	65
73	300	61	295	98	64	284	95	65
77	303	61	297	98	62	284	94	64
81[b]	300	57	301	100	55	283	94	59
85	306	54	302	99	55	283	93	57
89	307	52	305	99	55	287	94	53
93	307	49	305	99	53	286	93	49
97	303	46	304	100	50	281	93	43
101	291	44	296	102	47	271	93	39
105[b]	288	37	295	103	43	271	94	33
109	290	32	288	99	28	273	94	26
113	289	24	273	94	24	260	90	23
117	283	18	264	93	18	256	90	21
121	277	13	264	95	14	231	84	13
123	268	13	260	97	13	231	86	10
Terminal sacrifice		12			13			9
Mean for weeks								
1-13	156		159	102		156	100	
14-52	225		229	102		223	99	
53-123	291		288	99		271	93	

[a] The number of animals weighed for this week is fewer than the number of animals surviving.
[b] Interim evaluations occurred during weeks 27, 47, 79, and 105.

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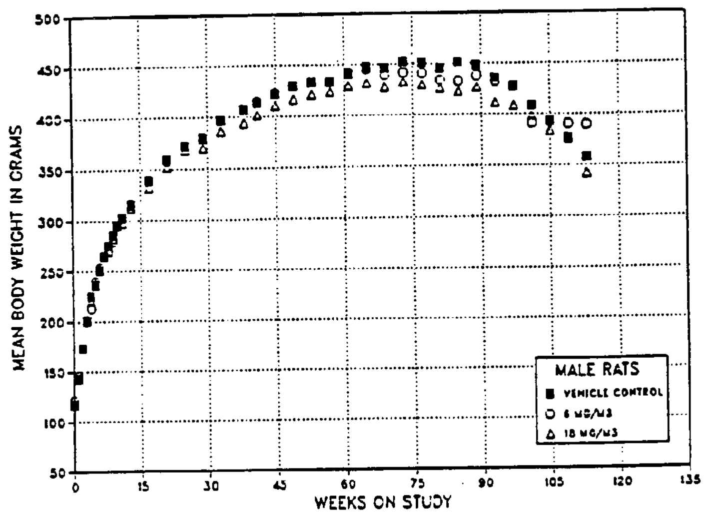


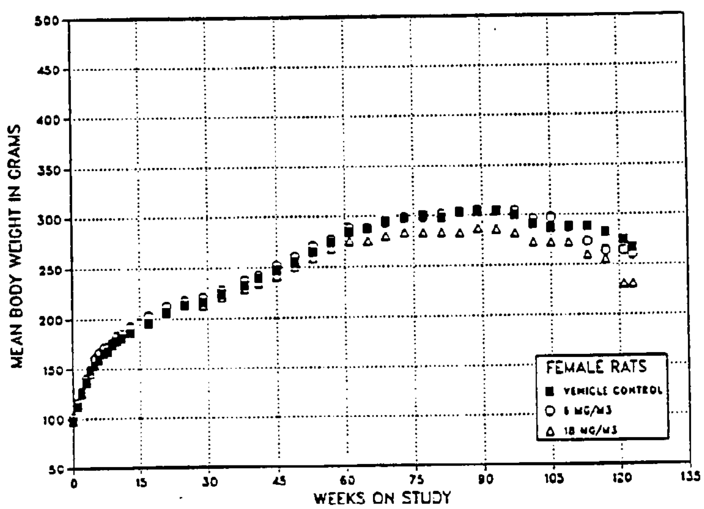


FIGURE 2
Growth Curves for Male and Female Rats Administered Talc by Inhalation for Their Lifetime

Lung: Absolute and relative lung weights of male rats exposed to 18 mg/m³ were significantly greater than those of controls at the 6-, 11-, and 18-month interim evaluations and at the end of the study, while those of female rats exposed to 18 mg/m³ were significantly greater than those of controls at the 11-, 18-, and 24-month interim evaluations and at the end of the study (Appendix E). Although lung weights of males exposed to 6 mg/m³ were not significantly different from controls at any of the interim evaluations, those of females at the 18-month interim evaluation and at the end of the lifetime study were significantly greater.

Pulmonary lesions in male and female rats occurring in response to the inhalation of talc aerosols were generally similar at the interim evaluations and the end of the study, but varied in incidence, extent, and severity with exposure concentration and duration (Table 5). At necropsy, the lungs of exposed rats had multiple small, round, pale white lesions visible through the visceral pleura. These lesions were generally larger and more extensive in rats exposed to 18 mg/m³ than in those exposed to 6 mg/m³, and at the end of the study than at the earlier interim evaluations.

At the 6-month interim evaluation, the pulmonary lesions consisted of multiple, focal accumulations of alveolar macrophages and infrequent neutrophils within alveolar lumens (inflammation, granulomatous). When viewed under polarized light, the cytoplasm of the alveolar macrophages contained birefringent particles believed to be talc. In two female rats, the alveolar epithelium in some affected areas had increased numbers of low cuboidal type II pneumocytes (alveolar epithelial hyperplasia), but there was no apparent increase in the amount of collagen within the alveolar septa. The peribronchial lymphoid aggregates of several rats also contained focal accumulations of macrophages that varied from a few to approximately 10 cells in the plane of section (peribronchial hyperplasia, histiocytic).

In contrast to the first interim evaluation, hyperplasia of type II pneumocytes was associated with the intra-alveolar accumulations of macrophages in all exposed rats examined at 11 months. Moreover, in the most severely affected foci, the alveolar septa were thickened by the accumulation of reticulin and collagen fibers (interstitial fibrosis). The lesions in rats examined at 18 and 24 months and in core study rats were similar but generally larger and more extensive (Plates 1 and 2). Although alveolar macrophages predominated in the inflammatory lesions, varying numbers of neutrophils were also present and the interstitium contained infiltrates of mononuclear inflammatory cells (lymphocytes and macrophages). Moreover, epithelioid macrophages and multinucleated giant cells were also seen within foci of inflammation at these later time points. In some rats, there were well-delineated areas of fibrosis that completely obliterated the alveoli (Plates 3 and 4). Hyperplasia of the alveolar epithelium was often prominent at the margins of these lesions. The affected cells were cuboidal or columnar with prominent nucleoli and exhibited some pleomorphism.

In addition to the changes described above, squamous metaplasia of the alveolar epithelium (Plate 5) was observed in two male and eight female rats in the 18 mg/m³ groups of the core study (Table 5). The metaplasia was usually associated with inflammation and was characterized by the replacement of alveolar type I and type II pneumocytes by well-differentiated keratinized squamous cells. Squamous cysts were also seen in three males and seven females in the 18 mg/m³ groups and in one female in the 6 mg/m³ group. The cysts had outer walls of well-differentiated, stratified squamous epithelium without cellular atypia and central lumens often containing sloughed keratin.

Although an alveolar/bronchiolar adenoma was seen in one 6 mg/m³ female at the 18-month interim evaluation, the remainder of the pulmonary neoplasms were seen in rats in the core study (Table 6). The incidences of alveolar/bronchiolar adenoma, carcinoma, and adenoma or carcinoma (combined) in female rats exposed to 18 mg/m³ were significantly greater than those of controls. A squamous cell carcinoma was also observed in an 18 mg/m³ female. Alveolar/bronchiolar neoplasms occurred in two males exposed to talc aerosols, one at each of the exposure concentrations, and none were seen in control males. Because of the low number of affected male rats, these neoplasms could not be attributed to talc exposure.

Because of the moderate to marked hyperplasia of the alveolar epithelium associated with the inflammatory lesions and because of the fibrosis and

TABLE 5
Incidences of Selected Lung Lesions in Rats in the Lifetime Inhalation Study of Talc

	Male			Female		
	0 mg/m³	6 mg/m³	18 mg/m³	0 mg/m³	6 mg/m³	18 mg/m³
6-Month Interim Evaluation						
Lung[a]	3	3	3	3	3	3
Inflammation, Granulomatous[b]	0	3*(1.3)[c]	3*(2.3)	0	3*(1.3)	3*(3.0)
Peribronchial Hyperplasia, Histiocytic	0	1 (1.0)	2 (2.0)	0	1 (1.0)	2 (1.0)
Hyperplasia, Alveolar Epithelium	0	0	0	0	1 (1.0)	1 (1.0)
11-Month Interim Evaluation						
Lung	2	3	3	3	3	3
Inflammation, Granulomatous	0	3*(1.7)	3*(3.0)	0	3*(1.7)	3*(2.7)
Peribronchial Hyperplasia, Histiocytic	0	0	0	0	1 (1.0)	2 (1.5)
Hyperplasia, Alveolar Epithelium	0	3*(2.0)	3*(1.7)	0	3*(1.0)	3*(2.3)
Interstitium, Fibrosis, Focal	0	2 (1.0)	3*(1.0)	0	2 (1.0)	3*(1.0)
18-Month Interim Evaluation						
Lung	3	3	2	3	3	3
Inflammation, Granulomatous	1 (1.0)	3 (1.3)	2 (2.0)	0	3*(1.7)	3*(2.0)
Peribronchial Hyperplasia, Histiocytic	0	2 (1.0)	2 (1.0)	0	1 (1.0)	2 (1.0)
Hyperplasia, Alveolar Epithelium	1 (1.0)	3 (1.0)	2 (1.0)	1 (1.0)	3 (1.0)	3 (1.3)
Interstitium, Fibrosis, Focal	0	3*(1.0)	2 (1.5)	0	3*(1.3)	3*(1.7)
Alveolar/bronchiolar Adenoma	0	0	0	0	1	0
24-Month Interim Evaluation						
Lung	3	6	2	5	9	3
Inflammation, Granulomatous	0	6*(1.5)	2 (2.0)	1 (1.0)	9**(1.4)	3 (1.7)
Peribronchial Hyperplasia, Histiocytic	0	1 (1.0)	1 (2.0)	0	2 (1.0)	0
Hyperplasia, Alveolar Epithelium	0	6*(1.0)	2 (1.5)	1 (1.0)	9**(1.4)	2 (2.3)
Interstitium, Fibrosis, Focal	0	5*(1.0)	2 (1.5)	0	8**(1.4)	3*(3.0)
Core Study						
Lung	49	50	50	50	48	50
Inflammation, Granulomatous	2 (1.0)	50**(1.6)	49**(2.3)	2 (1.5)	47**(1.5)	50**(2.8)
Peribronchial Hyperplasia, Histiocytic	0	12**(1.3)	8**(1.9)	0	8**(1.3)	9**(1.3)
Alveolar Epithelium, Hyperplasia	5 (2.0)	26**(1.3)	38**(1.7)	2 (1.0)	27**(1.2)	47**(2.1)
Alveolus, Metaplasia, Squamous	0	0	2 (1.0)	0	0	8**(1.1)
Interstitium, Fibrosis, Focal	1 (1.0)	16**(1.2)	33**(1.8)	1 (1.0)	24**(1.5)	44**(2.1)
Cyst (Squamous)	0	0	3	0	1	7**

* Significantly different ($P \leq 0.05$) from the control by Fisher's exact test (interim evaluation) or logistic regression (lifetime study)
** $P \leq 0.01$
a Number of animals with lung examined microscopically.
b Number of animals with lesion.
c Average severity grades of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

TABLE 6
Incidences of Lung Neoplasms in Rats in the Lifetime Inhalation Study of Talc

	Male			Female		
	0 mg/m³	6 mg/m³	18 mg/m³	0 mg/m³	6 mg/m³	18 mg/m³
Core Study						
Alveolar/bronchiolar Adenoma						
Overall rates[a]	0/49 (0%)	1/50 (2%)	1/50 (2%)	1/50 (2%)	0/48 (0%)	9/50 (18%)
Terminal rates[b]	0/9 (0%)	0/14 (0%)	1/16 (6%)	0/11 (0%)	0/13 (0%)	1/9 (11%)
First incidence (days)	–[d]	781	799 (T)	805	–	716
Logistic regression[c]	P=0.494	P=0.527	P=0.615	P<0.001	P=0.503N	P=0.010
Alveolar/bronchiolar Carcinoma						
Overall rates	0/49 (0%)	0/50 (0%)	1/50 (2%)	0/50 (0%)	0/48 (0%)	5/50 (10%)
Terminal rates	0/9 (0%)	0/14 (0%)	1/16 (6%)	0/11 (0%)	0/13 (0%)	3/9 (33%)
First incidence (days)	–	–	799 (T)	–	–	828
Logistic regression	P=0.370	–[e]	P=0.615	P=0.003	–	P=0.028
Alveolar/bronchiolar Adenoma or Carcinoma						
Overall rates	0/49 (0%)	1/50 (2%)	1/50 (2%)	1/50 (2%)	0/48 (0%)	13/50 (26%)
Terminal rates	0/9 (0%)	0/14 (0%)	1/16 (6%)	0/11 (0%)	0/13 (0%)	4/9 (44%)
First incidence (days)	–	781	799 (T)	805	–	716
Logistic regression	P=0.494	P=0.527	P=0.615	P<0.001	P=0.503N	P<0.001
Squamous Cell Carcinoma						
Overall rates	0/49 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/48 (0%)	1/50 (2%)

(T) Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals examined microscopically.
[b] Observed incidence at terminal kill
[c] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard these lesions as nonfatal. A lower incidence in a dose group in indicated by N.
[d] Not applicable; no tumors in animal group
[e] Value of statistic cannot be computed.

inflammation occurring within some of the neoplasms, there was considerable difficulty in determining the biological nature of the proliferative lesions observed and in distinguishing hyperplasia from adenoma and adenoma from carcinoma. The adenomas were irregular, circumscribed masses consisting of cuboidal to columnar epithelium arranged in alveolar, tubular, or papillary formations and separated by varying amounts of collagenous connective tissue. The neoplastic epithelium generally formed a single layer and was relatively uniform with minimal cellular atypia. The carcinomas were distinguished from the adenomas on the basis of having greater cellular pleomorphism and atypia, but they exhibited little evidence of invasion and none metastasized (Plates 6 and 7). In several benign and malignant neoplasms, the central portion of the mass was composed primarily of dense collagen and the epithelial component was located at the periphery. The extent of fibrosis in these neoplasms is not typical of spontaneous alveolar/bronchiolar neoplasms in control F344/N rats. The fibrous connective tissue was not interpreted as being a primary scirrhous response to the neoplastic epithelium, but rather a component of the prolonged inflammatory reaction to talc.

Lymph node: Histiocytic hyperplasia, consisting of accumulations of macrophages in the subscapular and medullary sinuses, occurred in the bronchial lymph nodes (male: 0 mg/m³, 0/41; 6 mg/m³, 44/48; 18 mg/m³, 46/49; female: 0/46, 40/47, 45/47) and in the mediastinal lymph nodes (male: 0/48, 40/49, 43/47; female: 0/47, 33/44, 40/47) of rats exposed to talc (Tables A4 and B4). The macrophages had foamy cytoplasm filled with birefringent particles of talc.

Nose: Hyperplasia of the respiratory epithelium of the nasal mucosa occurred in three male rats exposed to 6 mg/m^3 and 14 male rats exposed to 18 mg/m^3, but not in the control group (Table A4). The lesion consisted of an increase in the number of goblet cells primarily in the mucosa of the nasal septum. Hyperplasia of the respiratory epithelium also occurred in several female rats, but the incidences in the exposed groups were not significantly increased (Table B4).

During the pathology review process, it was noted that male and female rats in control and exposed groups had large eosinophilic droplets in the cytoplasm of the olfactory and, to a lesser extent, the respiratory epithelium. The lesion (cytoplasmic alteration) was focal or multifocal and usually located near the junction of the two epithelial types. Although present in the controls, the incidences were increased in exposed rats (males: 3/49, 18/48, 40/47; females: 5/48, 23/45, 46/48).

Adrenal medulla: Focal adrenal medulla hyperplasia or pheochromocytoma were observed in rats at the various interim evaluations, but the number of affected rats was too small to draw definitive conclusions. However, in the core study, benign, malignant, or complex (combined) pheochromocytomas occurred with a significant positive trend in male and female rats, and the incidences in the 18 mg/m^3 groups were significantly greater than those of controls by pairwise comparisons (Table 7). Moreover, bilateral pheochromocytomas were more frequent in exposed male rats than in controls (Tables A3 and B3). Although adrenal medulla hyperplasia occurred with similar frequency among exposed and control female rats, the incidences of hyperplasia in exposed males were significantly lower than controls. The lower incidences in exposed males are possibly due, in part, to the reduced amount of normal medullary tissue (e.g., medullary tissue without a pheochromocytoma) in which to observe hyperplasia.

Focal hyperplasia and pheochromocytoma constitute a morphological continuum. Focal hyperplasia consisted of irregular, small foci of small to normal sized medullary cells arranged in packets or solid clusters slightly larger than normal; compression of the surrounding tissue was minimal or absent. Pheochromocytomas were generally larger than focal hyperplasia, caused variable compression of the surrounding parenchyma, and many obscured much or all of any remaining normal medullary tissue. The neoplastic cells were arranged in variably sized aggregates, large solid clusters, and/or trabecular cords several layers thick separated by a delicate fibrovascular stroma. The larger neoplasms usually exhibited greater cellular pleomorphism and atypia than smaller neoplasms. Because the only morphological criteria that unambiguously distinguish malignant from benign pheochromocytomas is frank invasion or metastasis, a diagnosis of malignant pheochromocytoma was made only when there was invasion of the capsule. Complex pheochromocytomas consisted of an admixture of neoplastic pheochromocytes and neuroblasts, ganglion cells, and/or Schwann cells.

Lung Talc Burden

The lung talc burdens of exposed rats, normalized to control lung weight or exposure level, are presented in Tables F2 and F3. The lung talc burden normalized to control lung weight (mg talc/g control lung) adjusts for differences in lung weight between sexes or at different ages. The lung burden normalized to control lung weight and exposure level (mg talc/g control lung/mg/m^3) adjusts for exposure level to determine the effect of exposure concentration on talc clearance from the lung.

The data, normalized to control lung weight, show that talc burdens of rats exposed to 6 mg/m^3 were similar between males and females and increased progressively from 6 to 24 months (Table F2). Lung talc burdens in females exposed to 18 mg/m^3 also increased progressively from 6 to 24 months. In contrast, lung talc burdens of males at the 18 mg/m^3 exposure concentration increased from 6 to 18 months, but remained about the same at 18 and 24 months.

The exposure-normalized data show that lung talc burdens were generally proportional to exposure concentration at each interim evaluation. The exposure-normalized lung burdens of rats exposed to 6 or 18 mg/m^3 were generally similar at each of the interim evaluations except for slight increases for males at 6 and 11 months and females at 6 months (Table F3). This suggests that either clearance of talc was not substantially impaired by increasing the exposure concentration, or that clearance of talc was impaired similarly at both exposure levels.

TABLE 7
Incidences of Nonneoplastic Lesions and Neoplasms of the Adrenal Medulla in Rats in the Lifetime Inhalation Study of Talc

	Male			Female		
	0 mg/m³	6 mg/m³	18 mg/m³	0 mg/m³	6 mg/m³	18 mg/m³
11-Month Interim Evaluation						
Adrenal Medulla[a]	2	3	3	3	3	3
Hyperplasia[b]	0	0	0	0	0	0
Pheochromocytoma, Benign	1	0	0	0	0	0
18-Month Interim Evaluation						
Adrenal Medulla	3	3	2	2	3	3
Hyperplasia	0	1 (1.0)[c]	0	0	1 (2.0)	1 (2.0)
Pheochromocytoma, Benign	0	0	1	0	0	0
24-Month Interim Evaluation						
Adrenal Medulla	3	6	2	5	9	3
Hyperplasia	2 (1.5)	2 (2.0)	0	3 (2.0)	0	0
Pheochromocytoma, Benign	0	2	0	0	4	0
Pheochromocytoma, Benign, Bilateral	1	1	2	0	1	3
Core Study						
Adrenal Medulla	49	48	47	48	47	49
Hyperplasia	20 (2.7)	8**(2.3)	9*(3.2)	22 (2.5)	20 (2.2)	16 (2.6)
Pheochromocytoma, Benign						
Overall rates[d]	25/49 (51%)	30/48 (63%)	36/47 (77%)	13/48 (27%)	14/47 (30%)	18/49 (37%)
Terminal rates[e]	6/9 (67%)	11/14 (79%)	16/16 (100%)	5/11 (45%)	5/13 (38%)	6/9 (67%)
First incidence (days)	429	558	614	678	705	697
Logistic regression test[f]	P=0.007	P=0.213	P=0.009	P=0.185	P=0.541	P=0.225
Pheochromocytoma, Malignant						
Overall rates	3/49 (6%)	3/48 (6%)	7/47 (15%)	0/48 (0%)	1/47 (2%)	10/49 (20%)
Terminal rates	1/9 (11%)	1/14 (7%)	3/16 (19%)	0/11 (0%)	0/13 (0%)	3/9 (33%)
First incidence (days)	670	544	645	-[g]	849	784
Logistic regression test	P=0.096	P=0.662	P=0.178	P<0.001	P=0.509	P=0.001
Pheochromocytoma, Complex						
Overall rates	0/49 (0%)	2/48 (4%)	1/47 (2%)	0/48 (0%)	0/47 (0%)	0/49 (0%)
Terminal rates	0/9 (0%)	1/14 (7%)	0/16 (0%)	0/11 (0%)	0/13 (0%)	0/9 (0%)
First incidence (days)	-	558	743	-	-	-
Logistic regression test	P=0.486	P=0.230	P=0.503	-[h]	-	-
Pheochromocytoma, Benign, Malignant, or Complex						
Overall rates	26/49 (53%)	32/48 (67%)	37/47 (79%)	13/48 (27%)	14/47 (30%)	23/49 (47%)
Terminal rates	7/9 (78%)	12/14 (86%)	16/16 (100%)	5/11 (45%)	5/13 (38%)	8/9 (89%)
First incidence (days)	429	544	614	678	705	697
Logistic regression test	P=0.007	P=0.147	P=0.006	P=0.014	P=0.541	P=0.024

* Significantly different ($P \leq 0.05$) from the control by logistic regression
** $P \leq 0.01$
a Number of animals with adrenal medulla examined microscopically.
b Number of animals with lesion.
c Average severity grades of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked
d Number of animals with neoplasm per number of rats with adrenal medulla examined microscopically.
e Observed incidence at terminal kill
f Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard these lesions as nonfatal.
g Not applicable; no tumors in animal group
h Value of statistic cannot be computed.

Pulmonary Function

Results of the respiratory function measurements are presented in Tables F9 through F41. A progressive dose and time-related impairment of respiratory function was observed in both male and female rats exposed to talc. The impairment was restrictive in nature, consisting of reduced lung volume, increased lung stiffness, reduced gas exchange efficiency, and nonuniform intrapulmonary gas distribution.

6-Month Interim Evaluation: At 6 months there were few significant differences between values for rats exposed to 18 mg/m^3 and controls, and no significant differences between values for rats exposed to 6 mg/m^3 and controls. There were, however, slight trends among both males and females toward smaller lung volumes and reduced forced expiratory flow. Total lung capacity, vital capacity, and forced vital capacity were all slightly smaller in the 18 mg/m^3 groups, but only the forced vital capacity of females differed significantly from controls. All forced expiratory flow rates were lower in the 18 mg/m^3 groups, but only those of males were significantly lower than those of the controls. The reduced flow rates were partly related to the smaller lungs, but even volume-normalized flow tended to be reduced in the exposed rats. The reduced flow rates most likely reflected changes in small airways. Total pulmonary resistance, which primarily reflects flow resistance in large airways, was unaffected.

11-Month Interim Evaluation: Functional alterations were clearly apparent in exposed males and females after 11 months. Total lung capacity, vital capacity, and forced vital capacity were significantly lower in males and females exposed to 18 mg/m^3 and males exposed to 6 mg/m^3. The reduced volume was accompanied by significant reductions in quasistatic lung compliance in males, and both dynamic and quasistatic lung compliance in females. The volume and compliance changes indicate a stiffening of the lung (or increase in elastic recoil). Forced expiratory flows during mid to late expiration were slightly lower in exposed males than in controls, but the differences were not significant.

A reduction of alveolar-capillary gas exchange efficiency was reflected by a significant reduction of carbon monoxide diffusing capacity in the 18 mg/m^3 male and female rat groups. Although diffusing capacity is somewhat volume dependent, the reduced lung volume did not completely account for the change. Volume-normalized diffusing capacity was also significantly reduced in male and female rats exposed to 18 mg/m^3.

18-Month Interim Evaluation: Total lung capacity, vital capacity, and forced vital capacity of all exposed groups of male and female rats were significantly lower than those of controls at 18 months, except for vital capacity of males exposed to 6 mg/m^3. In females exposed to 18 mg/m^3, these decreases were accompanied by significant increases in resting (functional residual capacity) and minimum (residual) volumes. The decrease in volume at maximum inflations (total capacity, vital capacity, and forced vital capacity) reflected the inability of the stiffened lungs to stretch normally. Volume-normalized forced expiratory flows of exposed male and female rats were generally greater than those of controls, due to the reduced lung volume and little or no reduction in flow.

All parameters of lung compliance in male and female rats exposed to 18 mg/m^3 were also significantly lower than controls at 18 months, while two of the three compliance parameters were significantly lower at the 6 mg/m^3 exposure level. The carbon monoxide diffusing capacities in males and females exposed to 18 mg/m^3 were significantly lower than controls at 18 months, which is consistent with the findings at 11 months.

The slope of phase III of the single-breath N_2 washout of male and female rats exposed to 18 mg/m^3 was significantly greater than controls, apparently due to uneven mixing of oxygen with residual nitrogen in the lung during maximal inflation. This finding reflects a nonuniform distribution of inhaled air.

24-Month Interim Evaluation: Because of reduced survival in all groups of male and female rats, fewer animals remained alive at 24 months for evaluation of pulmonary function. Because of the smaller group sizes (3 rats each from the control and 18 mg/m^3 groups were evaluated), few of the differences were statistically significant. Nevertheless, there were reductions in lung volume parameters (total lung capacity, vital capacity, and forced vital capacity), lung compliance, and carbon monoxide diffusing capacity in exposed male and female rats consistent with the findings at the earlier time periods.

The progression of the functional impairments over the course of the study are illustrated in Figure 3, which plots the data for three functional parameters obtained from the 3 male and 3 female rats in the 18 mg/m^3 exposure groups surviving until 24 months.

Bronchoalveolar Lavage and Lung Biochemistry

Following the completion of the pulmonary function tests at the 24-month interim evaluation, bronchoalveolar lavage was performed on the remaining rats in these groups and the lavage fluid was evaluated for enzymes, protein, and cell content as shown in Tables F4 and F5. Values for glucose-6-phosphate dehydrogenase and glutathione peroxidase are not reported because they were below the limits of detection.

The values for ß-glucuronidase, alkaline phosphatase, lactate dehydrogenase, and total protein in both male and female rats exposed to 18 mg/m^3 talc were significantly greater than those of controls. In addition, females in this group had a significantly higher value for glutathione reductase. Both male and female rats exposed to 6 mg/m^3 talc had significantly greater ß-glucuronidase values, but only female rats exposed to 6 mg/m^3 had higher values of alkaline phosphatase, lactate dehydrogenase, and protein. The percentages of polymorphonuclear leukocytes in the lavage fluid were also significantly greater in male and female rats exposed to talc at both concentration levels. The increase in enzymes, total protein, and leukocytes are consistent with the morphological findings of a chronic active inflammatory process and cellular degenerative changes.

The viability and phagocytic activity of alveolar macrophages recovered from the lungs of rats exposed to 6 or 18 mg/m^3 talc or from the chamber controls ranged from approximately 60% to 80%. Neither the viability or phagocytic activity were significantly affected by exposure to talc (Table F6).

Table F7 summarizes the effects of talc exposure on collagen metabolism and protein synthesis. Collagenous peptides in lavage fluid and collagen production (% newly synthesized protein) from female rats, but not males, exposed to 6 or 18 mg/m^3 were significantly greater than controls. Total lung collagen from males and females at both exposure levels were also significantly greater. Values for non-collagenous protein synthesis were significantly greater in males exposed to 6 or 18 mg/m^3 and in females exposed to 18 mg/m^3 than in controls.

Lung proteinase activity, as determined from lavage fluid and homogenate supernatant fluid, is shown in Table F8. Acid proteinase activity, primarily cathepsin D, was significantly greater in both males and females exposed to 6 or 18 mg/m^3 than in controls. Neutral proteinase activity in homogenate supernatant fluid was also greater in rats exposed to talc. The activity was mostly serine proteinase, like that of polymorphonuclear leukocyte elastase and cathepsin G.

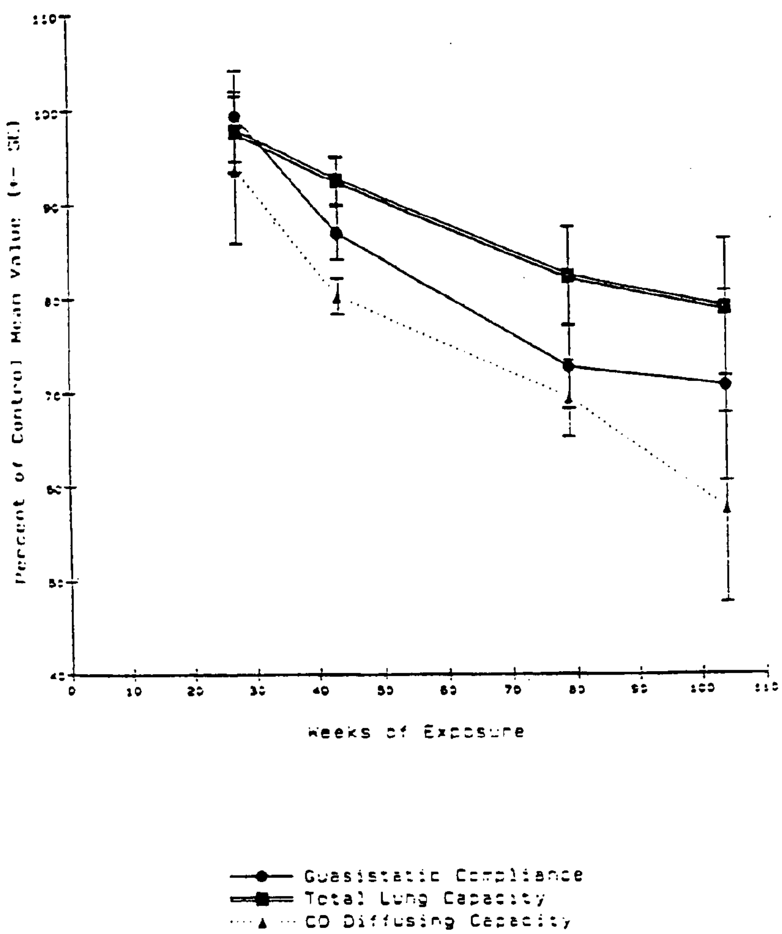


FIGURE 3
Effect of 18 mg/m³ Talc Exposure on Respiratory Function of Male and Female Rats Surviving to 104 Weeks

Mice

4-Week Study Dose Selection

Selection of 6 or 18 mg talc/m^3 as the exposure concentrations was based on the results of a 4-week inhalation study in B6C3F$_1$ mice to determine lung talc burden and histopathologic changes associated with talc exposure. These studies indicated that the amount of talc retained in the lung was similar between sexes and proportional to exposure concentration (Appendix K). Microscopic examination of the lungs revealed an accumulation of alveolar macrophages in the lungs only at 18 mg/m^3. Based on these findings it was predicted that aerosol concentrations greater than 18 mg/m^3 would overwhelm lung clearance mechanisms, impair lung function, and possibly shorten survival.

2-Year Study

Survival

Estimates of survival probabilities for male and female mice are shown in Table 8 and in the Kaplan-Meier curves in Figure 4. Survival of male and female mice exposed to talc was similar to that of the controls throughout most of the study. One female mouse exposed to 18 mg/m^3 died on day 20 and six others died on day 28 of the study of undetermined cause.

Body Weights and Clinical Findings

Mean body weights of male and female mice exposed to talc were similar to controls throughout the study (Tables 9 and 10, and Figure 5). There were no clinical findings in exposed mice that could be attributed to exposure to talc.

Prior to the start of the study and after 6 months of exposure, serological tests were negative for all viruses tested and *Mycoplasma spp*. At 12 months, 8/24 mice were positive for mouse hepatitis virus (MHV), but retesting of the serum by the enzyme linked immunosorbent assay (ELISA) showed all to be negative. At the end of the study, 7/30 were positive for *Mycoplasma arthritidis* and 21/30 were positive for epizootic diarrhea of infant mice (EDIM). No clinical signs or gross or microscopic evidence of disease associated with *M. arthritidis* was observed. EDIM does not cause clinical disease or pathology in adult mice.

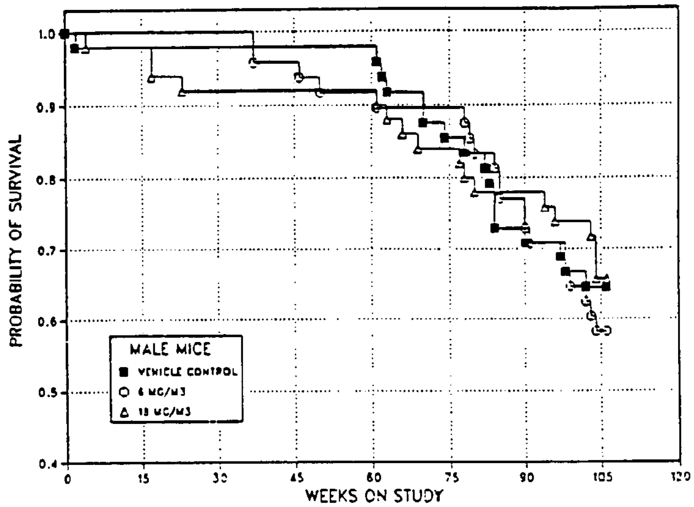
Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplastic or nonneoplastic lesions of the lung, lymph node, and nose. Summaries of the incidences of nonneoplastic lesions and neoplasms, the individual animal neoplasm diagnoses, and the statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one group are presented in Appendix C for male mice and Appendix D for female mice.

TABLE 8
Survival of Mice in the 2-Year Inhalation Study of Talc

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
Core Study Groups			
Animals initially in study	50	50	50
Natural deaths	16	18	14
Moribund kills	1	2	3
Missing[a]	2	1	1
Missexed[a]	1	1	0
Animals surviving to study termination	30	28	32
Percent survival at end of study[b]	65	58	66
Mean survival (days)[c]	648	648	645
Survival analysis[d]	P=0.886N	P=0.771	P=1.000N
Special Study Groups[a]			
Animals initially in study	39	40	40
Natural deaths	4	5	7
Moribund kills	0	1	1
Missing[a]	0	1	1
Scheduled sacrifice	35	33	31
Females			
Core Study Groups			
Animals initially in study	50	50	50
Natural deaths	17	21	21
Moribund kills	2	4	4
Missing[a]	1	1	0
Culled[a]	0	1	0
Animals surviving to study termination	30	23	25
Percent survival at end of study[b]	62	48	50
Mean survival (days)[c]	663	648	590
Survival analysis[d]	P=0.321	P=0.322	P=0.286
Special Study Groups[a]			
Animals initially in study	39	40	40
Natural deaths	7	5	10
Moribund kills	2	5	1
Scheduled sacrifice	30	30	29

[a] Censored from survival analyses
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice).
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the dosed columns. A negative trend or lower mortality in a dose group is indicated by N.



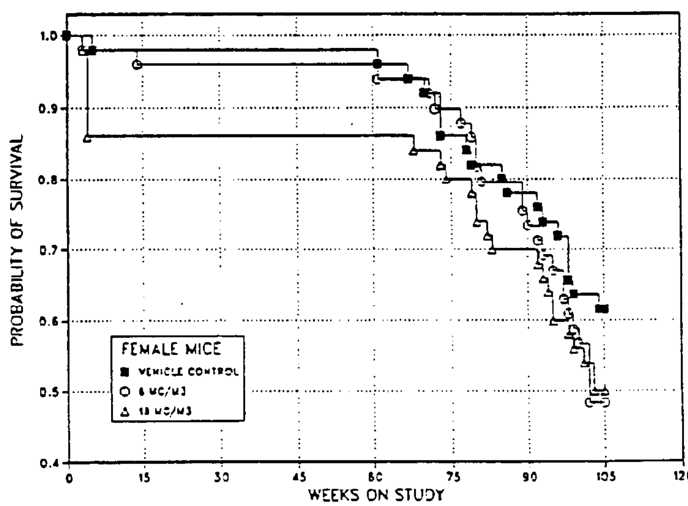


FIGURE 4
Kaplan-Meier Survival Curves for Male and Female Mice Administered Talc by Inhalation for 2 Years

TABLE 9
Mean Body Weights and Survival of Male Mice in the 2-Year Inhalation Study of Talc

Week on Study	0 mg/m³ Av. Wt. (g)	0 mg/m³ Number of Survivors	6 mg/m³ Av. Wt. (g)	6 mg/m³ Wt. (% of controls)	6 mg/m³ Number of Survivors	18 mg/m³ Av. Wt. (g)	18 mg/m³ Wt. (% of controls)	18 mg/m³ Number of Survivors
1	23.3	50	23.8	102	50	23.7	102	50
2	24.0	48	23.9	100	49	24.3	101	50
3	25.0	47	25.4	102	49	24.8	99	50
4	25.4	47	26.4	104	49	25.0	98	50
5	26.1	47	26.2	100	49	26.6	102	49
6	27.3	47	27.4	100	49	26.9	99	49
7	27.8	47	27.4	99	49	27.5	99	49
8	25.8	47	27.9	108	49	29.7	115	49
9	28.1	47	28.3	101	48	28.5	101	49
10	28.8	47	28.5	99	48	28.7	100	49
11	29.1	47	29.5	101	48	28.3	97	49
12	29.0	47	29.2	101	48	28.7	99	49
13	30.1	47	30.5	101	48	29.8	99	49
17	31.5	47	30.8	98	48	31.0	98	47
21	32.2	47	30.9	96	48	31.4	98	47
25	33.4	47	31.8	95	48	32.5	97	46
29	33.0	47	32.3	98	48	32.7	99	46
33	33.9	47	33.3	98	48	33.2	98	46
37	34.7	47	34.2	99	46	33.8	97	46
42	35.7	47	35.4	99	46	34.7	97	46
45	36.9	47	36.0	98	46	35.7	97	46
49	36.4	47	35.5	98	45	35.5	98	46
53	36.4	47	36.6	101	44	36.3	100	46
57	36.9	47	35.8	97	44	35.7	97	46
61	36.8	46	37.6	102	43	36.6	100	45
65	37.2	44	37.1	100	43	36.4	98	44
69	36.5	44	37.1	102	43	36.0	99	42
73	37.2	42	36.5	98	43	35.1	94	42
77	36.9	41	35.1	95	43	35.0	95	42
81	37.6	40	36.8	98	40	35.2	94	39
85	37.0	35	37.1	100	37	35.2	95	39
89	36.7	35	35.9	98	37	34.8	95	38
93	34.9	34	36.3	104	34	33.4	96	38
97	34.2	33	35.2	103	34	33.3	97	36
101	33.9	31	34.1	101	31	33.3	98	36
Terminal sacrifice		30			28			32
Mean for weeks								
1-13	26.9		27.3	101		27.1	101	
14-52	34.2		33.4	98		33.4	98	
53-101	36.3		36.2	100		35.1	97	

TABLE 10
Mean Body Weights and Survival of Female Mice in the 2-Year Inhalation Study of Talc

Week on Study	0 mg/m³ Av. Wt. (g)	0 mg/m³ Number of Survivors	6 mg/m³ Av. Wt. (g)	6 mg/m³ Wt. (% of controls)	6 mg/m³ Number of Survivors	18 mg/m³ Av. Wt. (g)	18 mg/m³ Wt. (% of controls)	18 mg/m³ Number of Survivors
1	19.3	50	19.3	100	50	19.6	102	50
2	19.9	50	20.1	101	50	20.5	103	50
3	21.0	50	21.3	101	50	21.1	101	50
4	22.4	50	22.5	100	49	21.5	96	49
5	22.5	49	22.7	101	49	23.2	103	43
6	24.4	49	23.7	97	49	23.8	98	43
7	24.6	49	24.5	100	49	24.3	99	43
8	22.1	49	24.2	110	49	26.8	121	43
9	24.6	49	24.9	101	49	25.2	102	43
10	25.2	49	25.4	101	49	25.3	100	43
11	25.6	49	26.2	102	49	25.0	98	43
12	25.5	49	25.1	98	49	25.2	99	43
13	26.3	49	26.4	100	49	25.9	99	43
17	27.5	49	26.7	97	47	27.3	99	43
21	28.4	49	27.2	96	47	27.7	98	43
25	29.5	49	28.1	95	47	28.9	98	43
29	29.8	49	28.6	96	47	28.9	97	43
33	30.1	49	29.7	99	47	29.5	98	43
37	30.7	49	29.9	97	47	29.9	97	43
42	31.7	49	30.8	97	47	30.3	96	43
45	32.4	49	31.7	98	47	31.1	96	43
49	32.2	49	31.2	97	47	31.0	96	43
53	32.7	49	31.4	96	47	31.9	98	43
57	32.7	49	31.0	95	47	31.2	95	43
61	33.1	49	32.9	99	46	32.3	98	43
65	33.0	48	32.4	98	46	32.7	99	43
69	32.7	47	32.4	99	46	32.1	98	42
73	32.8	43	32.1	98	44	31.0	95	41
77	32.6	43	31.3	96	43	31.3	96	40
81	33.5	41	32.7	98	39	32.1	96	37
85	32.5	40	33.0	102	39	32.7	101	35
89	32.7	39	32.1	98	36	32.1	98	35
93	31.7	37	31.7	100	33	31.2	98	33
97	31.5	35	31.7	101	30	30.6	97	30
101	31.8	31	31.4	99	27	31.0	98	27
Terminal sacrifice		30			23			25
Mean for weeks								
1-13	23.3		23.6	101		23.6	101	
14-52	30.3		29.3	97		29.4	97	
53-101	32.6		32.0	98		31.7	97	

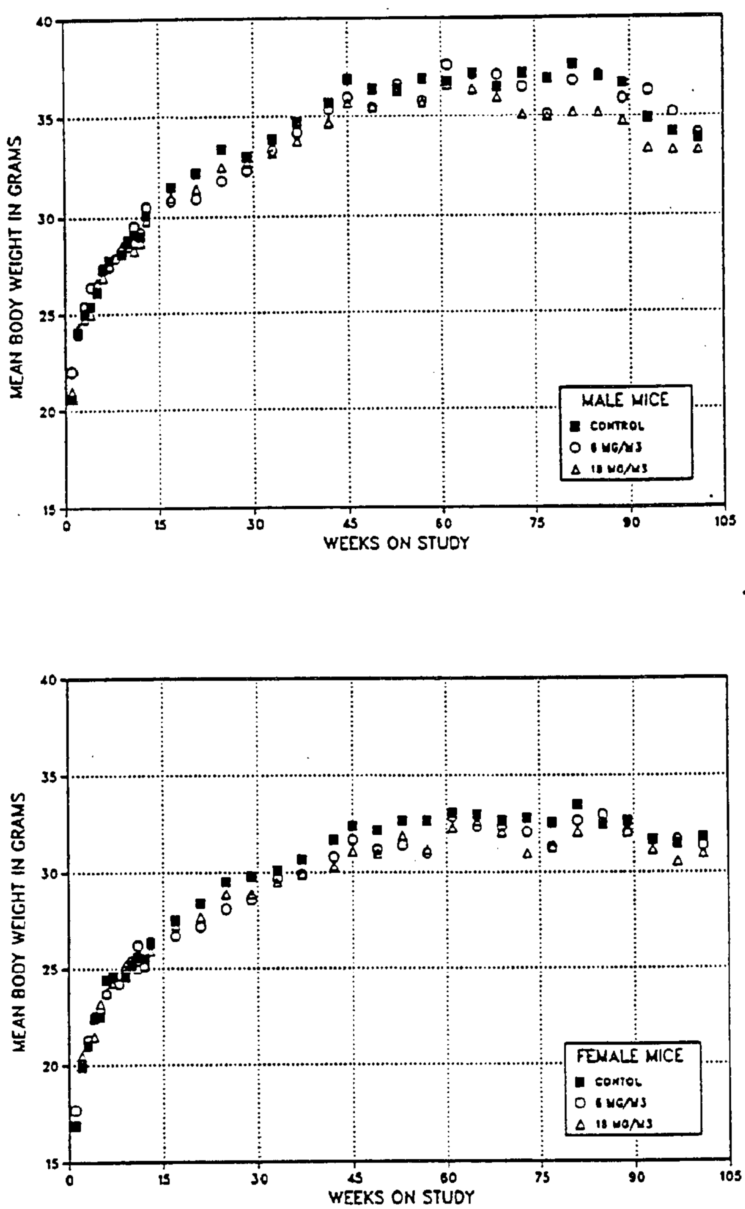


FIGURE 5
Growth Curves for Male and Female Mice Administered Talc by Inhalation For 2 Years

Lung: Absolute and relative lung weights of male and female mice exposed to 18 mg/m^3 talc were significantly greater at the 12- and 18-month interim evaluations and at the end of the study. Lung weights of mice exposed to 6 mg/m^3 were similar to controls at each of the interim evaluations.

The pulmonary lesions in mice exposed to talc were similar at the interim evaluations and at the end of the study, but the lesions varied in extent and severity with exposure concentration and duration (Table 11). The principal lung lesion occurring in exposed mice was an accumulation of alveolar macrophages in the alveoli surrounding terminal bronchioles (hyperplasia, macrophage) (Plate 8). The macrophages had abundant, slightly foamy to granular, eosinophilic cytoplasm containing birefringent talc particles. Small numbers of neutrophils were sometimes observed in the affected areas, and the interstitium contained infiltrates of mononuclear inflammatory cells (inflammation, chronic active) (Plates 9 and 10). In contrast to the pulmonary lesions in rats, hyperplasia of type II pneumocytes or fibrosis were not prominent components of the lesions in mice. The incidences of pulmonary neoplasms were similar among exposed groups and controls.

Lymph node: The bronchial lymph nodes of mice exposed to talc contained accumulations of macrophages in the medullary sinuses (hyperplasia, histocyte - male: 0 mg/m^3, 1/32; 6 mg/m^3, 32/39; 18 mg/m^3, 42/44; female: 0/38, 25/37, 39/43; Tables C4 and D4). The macrophages had abundant, slightly foamy to granular, eosinophilic cytoplasm filled with birefringent particles of talc.

Nose: The incidences of focal cytoplasmic alteration were increased in groups of mice exposed to talc (male: 5/45, 23/46, 40/47; female: 29/46, 37/46, 40/50; Tables C4 and D4). Focal cytoplasmic alteration was characterized by the formation of large eosinophilic droplets in the cytoplasm of olfactory and respiratory epithelial cells and was similar to that observed in rats.

Lung Talc Burden

The lung talc burdens, normalized to control lung weight or exposure level, are presented in Tables G2 and G3. Lung talc burden normalized to control lung weights (mg talc/g control lung) adjusts for differences in lung weight between sexes or at different ages. The lung burden normalized to control lung weight and exposure level (mg talc/g control lung/mg/m^3) adjusts for exposure level to determine the effect of exposure concentration on talc clearance from the lung.

The data, normalized to control lung weight, show that talc burdens of mice exposed to 6 mg/m^3 were similar between males and females and increased progressively from 6 to 24 months, except for males at 18 months (Table G2). However, because of the small sample size of males at 18 months (two animals), the lung talc burden of this sample may not be representative of the group as a whole. The lung talc burdens of mice exposed to 18 mg/m^3 were also similar between sexes at each interim evaluation. Although the talc burdens of males and females increased substantially from 6 to 24 months, the values at 12 and 18 months were similar.

The exposure-normalized data show that lung talc burdens of mice exposed to 18 mg/m^3 were disproportionately greater than those of mice exposed to 6 mg/m^3 (Table G2). The slight increases in exposure-normalized lung talc burden were statistically significant in males and females at 12 and 24 months, but not at 6 or 18 months. The lack of statistical significance at 18 months might be explained, in part, by the small sample size. These data suggest that clearance of talc from the lung was impaired, or impaired to a greater extent, in mice exposed to 18 mg/m^3 than in mice exposed to 6 mg/m^3.

Bronchoalveolar Lavage and Lung Biochemistry

Bronchoalveolar lavage was performed and lung homogenate supernatants collected for analyses at 6, 12, 18, and 24 months. A summary of the changes occurring in bronchoalveolar fluid enzymes, protein and cells are shown in Tables G4 through G22. Values for glucose-6-phosphate dehydrogenase, glutathione peroxidase, and alkaline phosphatase were not reported because they were below the limit of detection.

ß-Glucuronidase activity of lavage fluid from male and female mice exposed to 18 mg/m^3 was greater than that of controls at 12, 18, and 24 months, but not at 6 months. In mice exposed to 6 mg/m^3, ß-glucuronidase activity was greater than that of controls only at the 24-month interim evaluation. Lactate dehydrogenase and glutathione reductase activities in male and female mice exposed to

TABLE 11
Incidences of Nonneoplastic Lesions and Neoplasms in the Lung of Mice in the 2-Year Inhalation Study of Talc

	Male 0 mg/m³	Male 6 mg/m³	Male 18 mg/m³	Female 0 mg/m³	Female 6 mg/m³	Female 18 mg/m³
6-Month Interim Evaluation						
Lung[a]	4	4	4	4	4	4
Hyperplasia, Macrophage[b]	0	3 (1.0)[c]	4*(1.0)	0	0	4*(1.0)
Inflammation, Chronic Active	0	0	1 (1.0)	0	0	0
12-Month Interim Evaluation						
Lung	4	4	4	3	4	4
Hyperplasia, Macrophage	0	4*(1.0)	4*(1.8)	0	4*(1.0)	4*(2.0)
Inflammation, Chronic Active	0	0	2 (2.0)	0	0	1 (3.0)
18-Month Interim Evaluation						
Lung	4	4	4	4	4	4
Hyperplasia, Macrophage	0	4*(1.3)	4*(2.5)	0	4*(1.3)	4*(2.5)
Inflammation, Chronic Active	0	0	2 (1.5)	0	0	0
Alveolar/bronchiolar Adenoma	0	1	0	1	0	0
Alveolar/bronchiolar Carcinoma	1	0	0	0	0	0
2-Year Study						
Lung	45	47	48	46	48	50
Hyperplasia, Macrophage	3 (2.3)	46**(1.4)	48**(2.8)	2 (2.5)	45**(1.6)	43**(2.8)
Inflammation, Chronic Active	0	16**(1.1)	40**(2.2)	0	25**(1.4)	38**(2.3)
Alveolar Epithelium, Hyperplasia	1 (1.6)	0	0	0	0	1 (1.0)
Alveolar/bronchiolar Adenoma						
Overall rate[d]	6/45 (13%)	4/47 (9%)	9/48 (19%)	3/46 (7%)	2/49 (4%)	2/50 (4%)
Logistic regression[e]	P=0.251	P=0.411N	P=0.371	P=0.467N	P=0.499N	P=0.515N
Alveolar/bronchiolar Carcinoma						
Overall rate	7/45 (16%)	2/47 (4%)	2/48 (4%)	2/46 (4%)	4/49 (8%)	1/50 (2%)
Logistic regression	P=0.069N	P=0.073N	P=0.070N	P=0.325N	P=0.356	P=0.500N
Alveolar/bronchiolar Adenoma or Carcinoma						
Overall rate	12/45 (27%)	5/47 (11%)	11/48 (23%)	5/46 (11%)	6/49 (12%)	3/50 (6%)
Logistic regression	P=0.522N	P=0.043N	P=0.423N	P=0.269N	P=0.519	P=0.367N

* Significantly different (P≤0.05) from the control by Fisher's exact test (interim evaluation) or logistic regression (2-year study)
** P≤0.01
[a] Number of animals with lung examined microscopically.
[b] Number of animals with lesion.
[c] Average severity grades of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked
[d] Number of animals with neoplasm per number of mice examined microscopically.
[e] Beneath the controls incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the control and that dosed group. The logistic regression tests regard these lesions as nonfatal. A negative trend or a lower incidence in a dosed group is indicated by N.

18 mg/m^3 were significantly greater than those of controls at 18 and 24 months. Glutathione activity of males exposed to 18 mg/m^3 was also greater than controls at 12 months. Values for total protein in lavage fluid from males and females in the 18 mg/m^3 groups were significantly greater than controls at 18 months; at 24 months only that of males was significantly greater.

Significant differences in total and differential cell counts between exposed and control mice were observed only at 18 and 24 months at the high concentration level (Tables G8 to G11). The numbers of total nucleated cells, polymorphonuclear leukocytes, and macrophages were significantly greater in males and females exposed to 18 mg/m^3 than in controls. Exposure of mice to 6 or 18 mg/m^3 talc produced a concentration-related decrease in phagocytic activity of macrophages derived from lavage fluid (Tables G12 to G14). The number of macrophages containing phagocytized sheep erythrocytes from male and female mice exposed to 18 mg/m^3 was significantly lower than that from control mice at 12, 18, and 24 months. Although phagocytic activity of macrophages from mice exposed to 6 mg/m^3 was intermediate between controls and the high concentration groups, only the difference between the exposed and control males at 12 months was statistically significant.

The effects of talc exposure on lavage fluid collagenous peptides and total lung collagen are shown in Tables G15 through G18. The amount of collagenous peptides in lavage fluid from male mice exposed to 18 mg/m^3 was significantly greater than that of controls at 12, 18, and 24 months, while collagenous peptides of females exposed to 18 mg/m^3 were significantly increased only at 24 months. Consistent with these findings, total lung collagen was significantly greater in male mice at the high exposure concentration at 18 and 24 months and in females at 24 months. Collagenous peptides and total lung collagen from mice exposed to 6 mg/m^3 were similar to controls at each of the interim evaluations.

The acid and neutral proteinase activity of lung homogenate supernatant fluid and the acid proteinase activity of lavage fluid are shown in Tables G19 through G22. Although there were no consistent exposure-related changes in lavage fluid acid proteinase activity at any of the interim evaluations, acid proteinase activity in supernatant fluid from male and female mice exposed to 18 mg/m^3 was significantly greater than controls at 12, 18, and 24 months. The increase in acid proteinase activity was primarily due to cathepsin D-like activity. There were no consistent exposure-related changes in neutral proteinase activity at any of the interim evaluations.

DISCUSSION AND CONCLUSIONS

Talc ore may contain several other minerals including calcite, dolomite, magnesite, tremolite, anthophyllite, antigorite, quartz, pyrophyllite, micas, or chlorites. Since talc products are sold in a multitude of grades which have physical or functional characteristics especially suited for particular applications, occupational and consumer exposures to talc are complex. Exposure to industrial grade talc is known to cause pulmonary fibrosis, but the limited data on exposure to cosmetic grade talc are conflicting. Recently, epidemiology studies have revealed an association between nonfibrous talc and lung cancer risk (Thomas and Stewart, 1987). Talc was nominated by NIOSH for study by the NTP because of widespread human exposure and because of the lack of adequate information on its chronic toxicity and potential carcinogenicity.

The NTP toxicology and carcinogenicity studies of non-asbestiform, cosmetic grade talc, a finely powdered hydrous magnesium silicate, were conducted by exposing groups of male and female F344/N rats and $B6C3F_1$ mice to target aerosol concentrations of 0, 6 or 18 mg/m^3 talc for 6 hours daily, 5 days per week. Rats were exposed to talc until mortality in any group reached 80% (113 weeks for males and 122 weeks for females). Mice were exposed for 103 or 104 weeks. Exposure concentrations for the long-term studies were based on talc deposition and clearance patterns obtained from 4-week inhalation studies (Hanson *et al.*, 1985). In these studies, the amount of talc retained per unit of lung tissue was 79, 190, or 840 μg/g for male rats and 76, 185, or 770 μg/g for female rats exposed to 2, 6, or 18 mg/m^3. The amount of talc retained per unit of lung tissue in mice exposed at the same concentration levels were 130, 330, or 1,140 μg/g for males and 110, 330, or 1,160 μg/g for females. Only rats and mice at the highest exposure level had talc-containing macrophages within the alveolar spaces. Because there was a direct relationship between chamber concentration and lung talc burden and because of histologic evidence of a talc accumulation in alveolar macrophages at the 18 mg/m^3 concentration, it was predicted that higher levels would overwhelm lung clearance mechanisms in both species and cause deterioration of lung functions. Thus, 18 mg/m^3 was chosen as the top exposure concentration for the long-term studies.

The overall mean chamber concentrations achieved in the NTP long-term studies were 6.1 and 18.6 mg/m^3 for the rat study and 5.9 and 16.7 mg/m^3 for the mouse study. The average mass mean aerodynamic diameter of the talc particles was calculated to be 2.7 μm and 3.2 μm for the 6 and 18 mg/m^3 rat chambers and 3.3 μm and 3.6 μm for the 6 and 18 mg/m^3 mouse chambers, respectively. Seventy-five percent of the talc particles counted in four samples were in the 1 to 3 μm range. It has been shown, using aerosols of monodisperse aluminosilicate particles, in rats that particles larger than 10 μm are nearly all removed by inertial impaction in the nasal chamber or at bifurcation of the airways, while the percentage of particles deposited in the alveolar ducts and alveoli rises from almost zero at 10 μm to about 10% at about 1 μm (Raabe *et al.*, 1977) Thus, the large proportion of talc particles in these NTP studies were in the respirable range.

Because of difficulties with the aerosol concentration monitoring system for the 18 mg/m^3 rat chamber, there was a 7-week period beginning at study week 11 during which the chamber concentration for the high-dose rats varied from approximately 30 to 40 mg/m^3. Further, there was a 12-week period beginning at approximately week 70 during which there were difficulties in generating the talc aerosol and the chamber concentrations for rats and mice were substantially lower than the target concentrations (Figures H5 to H8). Although the exposure concentrations varied substantially from target concentrations during these periods, this does not preclude drawing conclusions regarding the chronic toxicity and carcinogenicity of talc. Since talc is a relatively inert particle, the amount of talc deposited and retained at the target site (lung talc burden) is a more relevant measure of talc exposure than chamber concentration. The problems with maintaining the target concentrations in the NTP studies did not have any apparent substantive effect on lung talc burdens.

The lung talc burden represents the difference between the amount of talc deposited in the lung and the amount removed by the clearance mechanisms. Inhaled particles deposited on the mucosal surface of the trachea, bronchi, or bronchioles are transported up the airways and from the lung through the ciliary activity of the respiratory epithelium, while particles reaching the alveolar region are phagocytized by alveolar macrophages and, to a lesser extent, other phagocytic inflammatory cells. Some of the alveolar macrophages migrate to the ciliated epithelium of the airways while others cross the alveolar lining to enter the interstitium and finally the lymphatics. Phagocytic cells reaching the lymphatics are transported in the lymph to the bronchial and mediastinal lymph nodes. Depending on the physiochemical properties of the inhaled particles, they may be partially or completely broken down within phagolysosomes of the macrophages and soluble components released from the cell. Talc is insoluble in water, cold acids, and alkalies and is likely to be insoluble in biological fluids. Talc particles were observed within macrophages in the lung and bronchial and mediastinal lymph nodes of rats and mice in these inhalation studies.

The lung talc burden of rats was greater than that of mice at each of the exposure concentrations and interim evaluations. The difference in lung talc burden is most likely related to anatomical and physiological differences known to influence particle deposition and retention including air flow pattern and velocity, respiratory rate, tidal volume, and clearance rate (McMahon *et al.*, 1977; Raabe *et al.*, 1977). The lung talc burdens of exposed rats and mice were generally similar between males and females at each exposure concentration and increased progressively with exposure duration. This indicated that the amount of talc deposited in the lung exceeded the clearance from the lung. The lung talc burden of rats was also generally proportional to exposure concentration at each interim evaluation, indicating that clearance of talc was not substantially impaired by increasing the exposure concentration, or that clearance of talc was impaired similarly at both exposure levels. In contrast, the lung talc burden of mice exposed to 18 mg/m^3 was disproportionately greater than that of mice exposed to 6 mg/m^3, indicating that clearance of talc from the lung was impaired, or impaired to a greater extent, in mice exposed to the higher concentration.

Analysis of bronchoalveolar lavage fluid has been used in human medicine for diagnosing the type or stage of various forms of interstitial lung disease and more recently as a rapid *in vivo* method of evaluating lung injury in toxicologic studies (Henderson *et al.*, 1985). Bronchoalveolar lavage was performed on rats and mice exposed to talc to evaluate its usefulness in chronic toxicology studies. Qualitatively similar changes in lavage fluid enzymes and cytology were observed in both species. Increases in neutrophils and total protein in lavage fluid are sensitive indicators of inflammation, and the increases in these parameters in rats and mice exposed to talc are consistent with the inflammation observed histologically in the lungs. Increases in cytoplasmic (lactate dehydrogenase and glutathione reductase) and lysosomal (ß-glucuronidase) enzymes, which are indicative of cellular injury, were also observed in both species. Whether lactate dehydrogenase and glutathione reductase were derived from parenchymal cells or inflammatory cells is unknown. The increase in glutathione reductase suggests that cellular injury may have involved an oxidative process involving free radicals produced during phagocytosis.

The phagocytic ability of alveolar macrophages recovered from lavage fluid was not impaired in rats exposed to talc for 24 months, as indicated by the lack of a significant difference in the number of viable macrophages and the percentage of cells phagocytizing sheep erythrocytes in exposed and control rats. In contrast, both the viability and the phagocytic ability of alveolar macrophages from exposed mice were significantly lower than those of macrophages from controls. The percent of macrophages containing phagocytized erythrocytes decreased as aerosol concentration and exposure duration increased. Since alveolar macrophages play a major role in the clearance of particles from the lung, the decreased viability and phagocytic ability of these cells may explain the disproportionately greater lung talc burden in mice exposed to 18 mg/m^3 than in mice exposed to 6 mg/m^3, and the difference in talc lung burdens between exposed rats and mice.

Due to limitations in chamber size and the number of animals that could be exposed, the numbers of animals utilized in the lung biochemistry studies were generally small. Therefore, some of the apparent inconsistencies in the results of these studies can be attributed to the small sample sizes as well as the biologic variation in pulmonary response among individuals. Despite these limitations, increases in lavage fluid collagenous peptides and total lung collagen were observed in both rats and mice exposed to 18 mg/m^3 talc. In rats, these

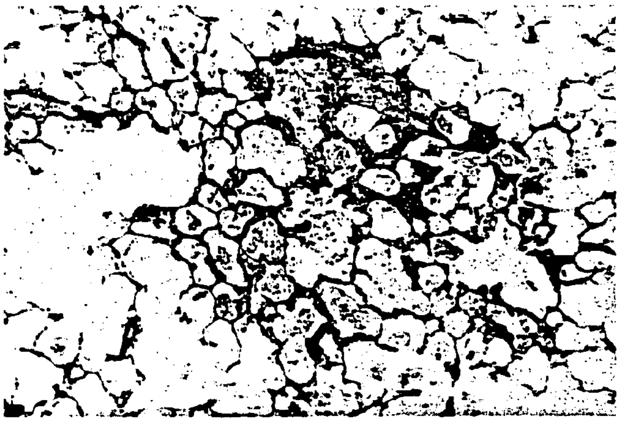


PLATE 1
Mild focal inflammation with thickening of the alveolar septa and distortion of the alveoli in lung of a male F344/N rat exposed to 18 mg/m^3 talc at the 18-month interim evaluation of the lifetime inhalation study. H&E, 25X

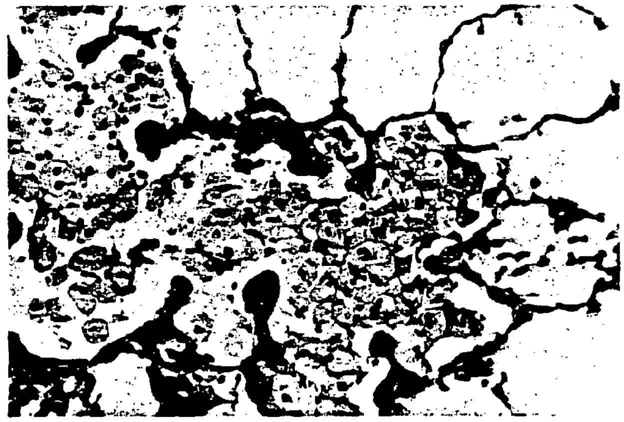


PLATE 2
Lung of a male F344/N rat exposed to 18 mg/m^3 talc at the 18-month interim evaluation of the lifetime inhalation study. Note the accumulation of alveolar macrophages with pale granular cytoplasm in the alveolar duct and slight thickening of the septal walls. H&E, 80X

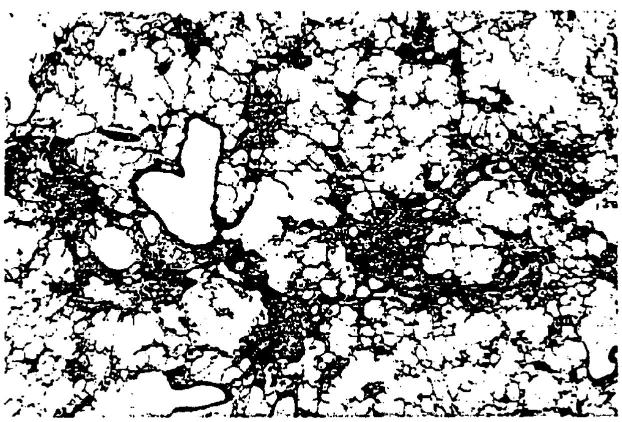


PLATE 3
Individual and confluent foci of interstitial fibrosis extend throughout the pulmonary parenchyma of a male F344/N rat exposed to 18 mg/m^3 talc at the 24-month interim evaluation of the lifetime inhalation study. H&E, 6.6X

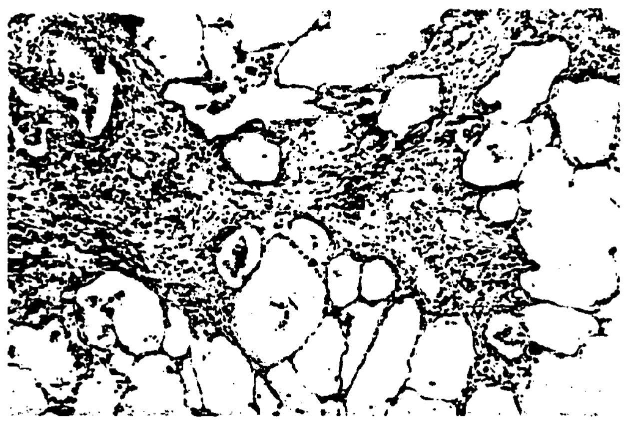


PLATE 4
Higher magnification of Plate 3 showing accumulation of fibrous tissue and interspersed inflammatory cells which obliterate the alveoli. H&E, 33X

Plate 5

Squamous metaplasia and hyperplasia of the alveolar epithelium adjacent to an area of chronic inflammation and interstitial fibrosis in the lung of a male F344/N rat exposed to 18 mg/m³ talc in the lifetime inhalation study. H&E, 40X

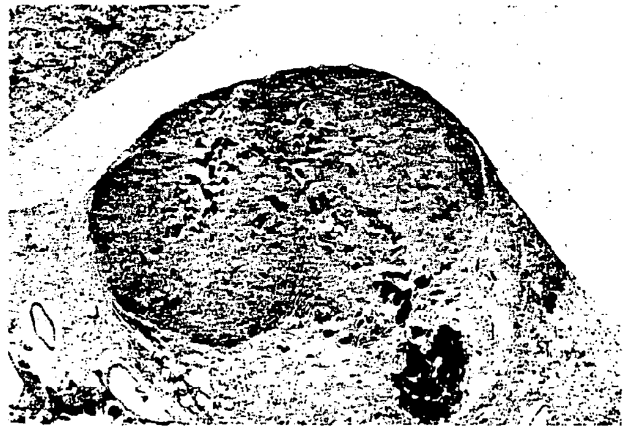


Plate 6

Alveolar/bronchiolar carcinoma in a male F344/N rat exposed to 18 mg/m³ talc in the lifetime inhalation study. Note the large mass obliterating the pulmonary parenchyma. H&E, 2.5X

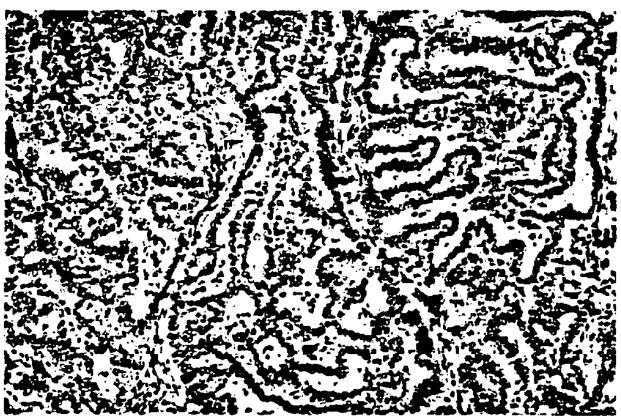


Plate 7

Higher magnification of the alveolar/bronchiolar carcinoma in Plate 6 showing neoplastic epithelium arranged in irregular papillary formations. H&E, 50X

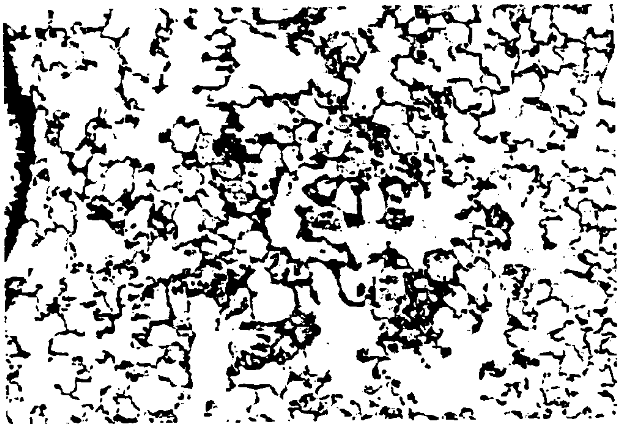


PLATE 8
Minimal focal accumulation of alveolar macrophages in the lung of a male B6C3F$_1$ mouse exposed to 18 mg/m^3 talc at the 12-month interim evaluation of the 2-year inhalation study. H&E, 50X

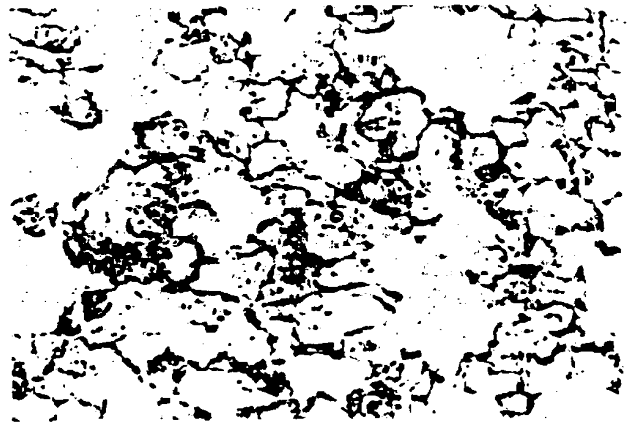


PLATE 9
Mile chronic active inflammation with slight thickening of the alveolar septa in the lung of a female B6C3F$_1$ exposed to 18 mg/m^3 talc in the 2-year inhalation study. H&E, 50X

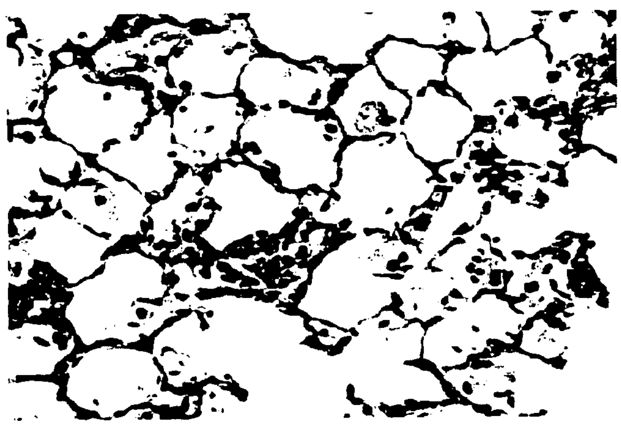


PLATE 10
Alveolar macrophages in alveoli and mononuclear cells in the interstitium of the lung of a male B6C3F$_1$ mouse exposed to 18 mg/m^3 talc in the 2-year inhalation study. H&E, 100X

changes were also accompanied by increases in noncollagenous protein synthesis (total ^{14}C-proline incorporated into lung tissue minus that incorporated into collagen), and, in females only, an increase in collagen production (% of total ^{14}C-proline incorporated into collagen). Some parameters were also significantly increased in rats exposed to 6 mg/m^3 talc. While these results are consistent with the fibrosis observed histologically in rats, fibrosis was not seen histologically in mice.

Talc exposure was associated with a dose- and time-related impairment of respiratory functions in male and female rats. Although only slight trends were observed at 6 months in rats exposed to 18 mg/m^3 talc, functional alterations in rats at the high concentration were clearly evident after 11 months. In rats exposed to 6 mg/m^3, decrements in respiratory function were observed in males at 11 months and in males and females at 18 months. The functional impairment was characterized by reduced lung volumes and reduced dynamic and/or quasistatic lung compliance, indicating an increase in elastic recoil (increased lung stiffness). Further, reduced gas exchange efficiency and nonuniform intrapulmonary gas distribution were also observed. These changes are consistent with the multifocal fibrosis and inflammation that was centered around the centriacinar region of the lung.

Deposition of talc in the lungs of rats and mice produced an inflammatory response characterized primarily by the accumulation of alveolar macrophages and, to a lesser extent, neutrophils and monocytes within alveolar lumens. Smaller numbers of lymphocytes and plasma cells were also observed in the interstitial tissue surrounding airways, blood vessels, and alveolar septa. The lesions developed at the junction of the alveolar ducts and terminal bronchioles where particles of the size range used are known to be deposited (Brody and Roe, 1983). Although the inflammatory response was basically similar in rats and mice, there were important species differences. The lesions in rats were generally more extensive and more severe than those in mice at similar exposure concentrations. In rats, foreign body giant cells were occasionally seen and some of the alveolar macrophages developed the morphological characteristics of epithelioid macrophages. More importantly, the inflammatory lesions in rats were accompanied by interstitial fibrosis, hyperplasia of alveolar epithelial type II cells, and, infrequently, squamous metaplasia of the alveolar epithelium.

The differences in pulmonary response cannot be attributed to differences in lung talc burden, since fibrosis and alveolar epithelial hyperplasia were seen in rats exposed to 6 mg/m^3, which had lung talc burdens less than that of mice exposed to 18 mg/m^3. Saffiotti and Stinson (1988) have reported similar differences in pulmonary response between rats and mice following intratracheal instillation of silica. These authors found that silica-induced alveolar epithelial hyperplasia in mice was transient, returning to normal within several months, while that in rats was generally more severe and persisted until the end of the study. Since inhalation studies using both rats and mice are seldom performed, it is uncertain if this species difference might exist for other particulate substances.

The difference in pulmonary response between rats and mice may be related, in part, to species differences in reactivity of the alveolar macrophage following phagocytosis of the talc particles. As the principal phagocytic cell of the lung, the alveolar macrophage is believed to play a major role in the inflammatory and fibrogenic reactions to inhaled particles (Brain, 1980; Brody, 1991). Much of the early work in this area centered on the differential cytotoxicity of phagocytized particles, particularly the various crystalline forms of asbestos and silica, to alveolar macrophages and the subsequent release of lysosomal enzymes which have proteolytic, elastolytic, and inflammatory properties (Brody and Davis, 1982; Nathan, 1987). More recently, alveolar macrophages have been shown to produce arachidonic acid metabolites (Kouzan *et al.*, 1985) and various cytokines that regulate cell proliferation, differentiation, and extracellular matrix production (Kelley, 1990). Of particular interest, rat alveolar macrophages exposed to iron spheres and asbestos fibers have been shown to produce increased amounts of a homologue of platelet-derived growth factor (Bonner *et al.*, 1989, 1990), the most potent mitogen known for mesenchymal cells, and TGF-ß, a potent inhibitor of mesenchymal cell proliferation and stimulator of matrix production (Kalter *et al.*, 1989). Little is known about the putative role of PDGF and TGF-ß and other macrophage-derived products in the pathogenesis of lung disease, but they are likely to be important mediators of many cellular events.

The lesions in the lungs of rats exposed to aerosols of talc are very similar, qualitatively, to those reported to occur following long-term (approximately 2 years) exposure to other inorganic,

non-fibrous, particulate substances including titanium dioxide (Lee *et al.*, 1985), chromium dioxide (Lee *et al.*, 1988), antimony trioxide and antimony ore concentrate (predominantly antimony trisulfide) (Groth *et al.*, 1986), and volcanic ash (Wehner *et al.*, 1986). Aerosols of each of these particulate substances were reported to elicit pulmonary inflammation, characterized primarily by the accumulation of alveolar macrophages, hyperplasia and squamous metaplasia of the alveolar epithelium, and fibrosis. Since the various components of the pulmonary response were not quantified in these studies, there may be quantitative differences in the degree of inflammation, fibrosis, and cellular degenerative hyperplastic and metaplastic changes to these particulate substances.

The lesions in rats exposed to talc are also similar to those observed in rats exposed to silica, but with important differences. Silica generally produces an inflammatory response that is more pronounced and persistent than the response to the relatively more inert particles like titanium dioxide and talc (Saffiotti and Stinson, 1988; Driscoll *et al.*, 1990). Further, while only occasional multinucleated cells and epithelioid macrophages were seen in the cellular response to talc, rats exposed to silica develop discrete nodular aggregates of epithelioid macrophages with some multinucleated cells more typical of granulomatous inflammation.

The quantitative and qualitative differences in pulmonary toxicity to inhaled particles are likely related to their size, structure (amorphous, crystalline, and/or fibrous), surface chemistry, solubility (or durability), chemistry of soluble components, cytotoxicity, and other factors. While much of the research in this area has focused on asbestos (as well as other fibers) and silica, the same principles are likely to explain the differences in biological activity of other particulate substances. Although a complete discussion of these factors is beyond the scope of this report, some of the evidence is presented here.

A number of studies of the various forms of silicon dioxide have shown that amorphous silica produces the mildest, slowest developing pulmonary changes followed, in ascending order, by quartz, cristobalite and tridymite (Allison, 1977; Hemenway *et al.*, 1986). Amorphous silica generally lacks a detectable crystalline X-ray diffraction pattern, while, of the crystalline forms, quartz has a less ordered symmetry than cristobalite and tridymite. Moreover, stishovite, which lacks the tetrahedral structure of other forms of silica, also lacks the fibrogenicity and cytotoxicity of the other forms (Brieger and Gross, 1967).

In general, the ability of various forms of silica to elicit pulmonary fibrosis parallels their cytotoxicity *in vitro* to alveolar macrophages (Reiser and Last, 1979). Further, there is a correlation between cytotoxicity and hemolytic activity *in vitro* (Allison, 1977). The biochemical basis of macrophage cytotoxicity and hemolytic activity is not fully understood, but the surface of crystalline silica presents highly reactive hydroxyl groups of silicic acid residues (silanol) that act as proton-donors and may combine with constituents of cellular membranes (Langer and Nolan, 1986). Kaolinite (aluminum silicate), mica (potassium aluminum silicate), and talc (magnesium silicate) are also hemolytic *in vitro* (Narang *et al.*, 1977). Dissolution of silicic acid residues from kaolinite, mica, and talc reduces the toxicity of these particulates, supporting the hypothesis that the reactive hydroxyl groups play an important role in cytotoxicity and hemolytic activity.

Following phagocytosis of silica (Allison, 1977) or kaolinite (Brody and Davis, 1982) particles by alveolar macrophages, hydrolytic enzymes are released from secondary lysosomes apparently as a result of the interaction of the particles with the lysosomal membrane. While the release of lysosomal enzymes into the cytoplasm may be directly responsible for cell death, it is less clear to what extent lysosomal enzymes released from the cells contribute to the other pulmonary lesions. Certainly, the ability to kill alveolar macrophages (cytotoxicity) is likely to inhibit or delay removal of the particles from the lung, increase the lung burden, and allow other biological effects to occur.

As already mentioned, macrophages secrete a large number of molecules with a wide range of biological functions including polypeptide hormones or cytokines, complement components, coagulation factors, arachidonic acid and its metabolites, bioactive lipids (prostaglandins and leukotrienes), binding proteins, enzyme inhibitors, extracellular matrix or cell adhesion proteins, and others (for review see Nathan, 1987). Some, or perhaps many, of the apparent differences in the pulmonary response of rats to the various particulate substances may be related to the extent to which they cause cytotoxicity and nonspecific release of lysosomal enzymes or cause macrophages to secrete specific effector substances like the cytokines and inflammatory mediators.

Exposure of female rats to 18 mg/m^3 talc was associated with increased incidences of benign and malignant pulmonary neoplasms (alveolar/bronchiolar adenoma: 1/50, 0/48, 9/50; alveolar/bronchiolar carcinoma: 0/50, 0/48, 5/50; squamous cell carcinoma: 0/50, 0/48, 1/50). The overall incidence of alveolar/bronchiolar adenoma or carcinoma (combined) in female rats of the high-concentration group was significantly (P≤0.001) greater than that of controls (1/50, 0/48, 13/50). The incidence of pulmonary neoplasms in female rats exposed to 18 mg/m^3 also greatly exceeds that of control females (8/529, 1.5%) in the NTP lifetime studies reported by Solleveld *et al.* (1984). While comparison with the historical controls from NTP lifetime studies has some limitations (e.g., the studies were conducted about a decade ago and are not contemporary), such a comparison provides some perspective. The increased incidence of pulmonary neoplasms in the 18 mg/m^3 female rats was considered clear evidence of carcinogenic activity based on a) the strength of the statistical evidence (P≤0.001), b) the increase in malignant as well as benign neoplasms, and c) comparison with lifetime historical controls.

In contrast to female rats, there was no increase in the incidence of pulmonary neoplasms in male rats or in male or female mice exposed to talc aerosols. While precise comparisons between studies of talc and other particulate substances cannot be made because of differences in route of administration (intratracheal versus inhalation), strain of rat used, and exposure duration, such comparison provides some perspective (Table 12). The predilection of female rats over male rats for developing pulmonary neoplasms has also been observed in 2-year inhalation studies of titanium dioxide (Lee *et al.*, 1985), chromium dioxide (Lee *et al.*, 1988), antimony trioxide and antimony ore concentrate (predominantly antimony trisulfide) (Groth *et al.*, 1986), volcanic ash (Wehner *et al.*, 1986), and quartz (Dagle *et al.*, 1986). Chromium dioxide, volcanic ash, antimony trioxide, and antimony ore concentrate induced pulmonary neoplasms only in female rats, whereas titanium dioxide and quartz induced pulmonary neoplasms in males and females with a preponderance of neoplasms in females.

The morphological types of neoplasms induced by the particulates in the studies cited above also vary somewhat. The neoplasms in female rats exposed to talc were primarily alveolar/bronchiolar adenomas and carcinomas, although one squamous cell carcinoma also occurred. In female rats exposed to antimony trioxide or antimony ore concentrate (Groth *et al.*, 1986), there were similar numbers of alveolar/bronchiolar neoplasms and squamous cell carcinomas (Table 12). Further, several scirrhous carcinomas were seen in antimony exposed rats. In female rats exposed to titanium dioxide (Lee *et al.*, 1985), the incidences of alveolar/bronchiolar neoplasms and squamous cell carcinoma were also similar, whereas all but one of the neoplasms in males were alveolar/bronchiolar neoplasms. In contrast, nearly all the pulmonary neoplasms induced by quartz (Dagle *et al.*, 1986), volcanic ash (Wehner *et al.*, 1986) or chromium dioxide (Lee *et al.*, 1988) were squamous cell (epidermoid) carcinomas.

The pathogenesis of pulmonary neoplasms induced by the relatively insoluble particulate substances, such as talc, is currently unknown. Although a genotoxic mechanism cannot be ruled out, there are several facts and lines of evidence to suggest that a direct effect of the particulate on the target cell genome is not involved. First, the insoluble nature of these particulates makes it unlikely that any chemical constituents will reach sufficient concentration to affect the target cells within the relatively short period between the time they are deposited on the alveolar surface and the time they are phagocytized. Further, although occasional alveolar epithelial cells have been observed to contain particles following intratracheal or inhalation exposure (Sorokin and Brian, 1975; Lee *et al.*, 1979), the vast majority of particles are rapidly phagocytized by alveolar macrophages, some within minutes of deposition in the lung (Lauweryns and Baert, 1974). It is also clear that physical characteristics (crystalline structure, fiber dimension) and surface chemistry (presence of reactive groups on the particle surface), rather than soluble chemical components, are principle determinants of tissue reaction, and perhaps for carcinogenicity. The carcinogenicity of many fibrous materials (fiberglass, attapulgite, silicon carbide, mineral wool, and potassium titanate) decreases as fiber diameter exceeds 2.5 μm and as fiber length decreases below 10 μm (Stanton and Wrench, 1972; Stanton *et al.*, 1977).

A potential mechanism for the development of pulmonary neoplasms associated with insoluble particulate substances is that the prolonged stimulus for cell replication, due not only to cell injury but to the release of mitogenic growth factors from alveolar macrophages, provides a favorable

TABLE 12
Results of Selected Whole Body Inhalation Carcinogenicity Studies of Particulate Materials

Compound and Dose	Study Duration	Species	Effects[a]
Talc at 0, 6, or 18 mg/m^3 (NTP, 1992)	Male: 113 weeks Female: 122 weeks	F344/N rats	Females: alveolar/bronchiolar adenoma (1/50, 0/48, 9/50); alveolar/bronchiolar carcinoma (0/50, 0/48, 5/50); squamous cell carcinoma (0/50, 0/48, 1/50)
Titanium dioxide at 0, 10, 50, or 250 mg/m^3 (Lee *et al.*, 1985)	104 weeks	CD rats	Females: alveolar/bronchiolar adenoma (0/77, 0/75, 0/74, 13/74); squamous cell carcinoma (0/77, 0/75, 0/74, 13/74)
Titanium tetrachloride at 0, 0.1, 1.0, or 10 mg/m^3 (Lee *et al.*, 1986)	104 weeks	Crl:CD rats	Females: squamous cell carcinoma (0/77, 0/75, 0/79, 3/75); Males: squamous cell carcinoma (0/79, 0/77, 0/78, 2/75)
Chromium dioxide at 0, 0.5, 0.5[b], or 25 mg/m^3 (Lee *et al.*, 1988)	104 weeks	Sprague-Dawley rats	Females: squamous cell carcinoma (0/106, 0/103, 0/108, 2/108); keratin cyst (0/106, 0/103, 0/108, 6/108)
Antimony trioxide at 0 or 45 mg/m^3 (Groth *et al.*, 1986)	73 weeks	Wistar rats	Females: alveolar/bronchiolar neoplasms (0/90, 11/90); squamous cell carcinoma (0/90, 9/90); scirrhous carcinoma (0/90, 5/90)
Antimony trisulfide at 0 or 40 mg/m^3 (Groth *et al.*, 1986)	72 weeks	Wistar rats	Females: alveolar/bronchiolar neoplasms (0/90, 6/90); squamous cell carcinoma (0/90, 9/90); scirrhous carcinoma (0/90, 4/90)
Volcanic ash at 0, 5, or 50 mg/m^3 (Wehner *et al.*, 1986)	up to 104 weeks	F344 rats	Females: several[c] squamous cell carcinomas in the 50 mg/m^3 group. Male: one squamous cell carcinoma in the 50 mg/m^3 group.
Quartz at 0 or 50 mg/m^3 (Wehner *et al.*, 1986)	up to 104 weeks	F344 rats	Females: moderate[c] numbers of squamous cell carcinomas in the 50 mg/m^3 group. Males: one squamous cell carcinoma in the 50 mg/m^3 group.

[a] Tumor incidences are given as the number of animals with tumor per number of animals examined. The incidences are given in the order of increasing exposure concentration.
[b] This dose represents unstabilized chromium dioxide; the other doses represent stabilized chromium dioxide.
[c] Precise numbers not available in journal article.

environment for the promotion and progression of spontaneously initiated cells. The interim evaluations in the NTP talc study clearly demonstrate a progressive impairment of homeostatic growth regulation in the areas of chronic inflammation and fibrosis associated with talc deposition in rats. Hyperplasia of the alveolar epithelium was evident at 6 months and became more extensive and severe with duration of exposure. Not only were there increased numbers of cells (hyperplasia), but some cells assumed morphologic features atypical of regenerating or differentiated type II cells (epithelial dysplasia). The altered or dysplastic epithelium was particularly evident in areas of fibrosis. The squamous metaplasia observed in female rats also represents altered differentiation of populations of alveolar epithelial cells and is notable in light of the development of squamous cysts and squamous cell carcinomas.

The lack of a carcinogenic effect in male rats or in mice exposed to talc aerosols does not negate the possibility of a mechanism as described above. First, the difference between male and female rats may be one of magnitude rather than an absolute difference in effect. The influence of the length of exposure on the development of these late appearing lung neoplasms cannot be discounted; the length of

exposure was 113 weeks for males and 122 weeks for females. Further, the promotion and progression of neoplasia involve a complex series of molecular events that are likely to differ qualitatively or quantitatively in males and females. Clearly, there are sex differences in the incidence of spontaneous and chemically induced neoplasms. As for mice exposed to talc, there was no histologic evidence of impaired growth regulation or fibrosis, consistent with the mechanism proposed above.

Pheochromocytomas (benign, malignant, or complex) of the adrenal medulla occurred with significant positive trends in both male and female rats exposed to talc (males: 26/49, 32/48, 37/47; females: 13/48, 14/47, 23/49). Further, the numbers of male and female rats with bilateral pheochromocytomas were also increased in the exposed groups. The overall incidences of this neoplasm in the 18 mg/m^3 exposure groups were significantly greater than those of the controls. Comparison with historical controls of NTP lifetime studies is not considered relevant, since there has been a pronounced increase in the spontaneous occurrence of pheochromocytomas in male rats in studies conducted by the NTP over the last 10 years (Rao *et al.*, 1990).

In contrast to the pheochromocytomas, the incidences of adrenal medulla hyperplasia in exposed male rats were lower than in controls, and the incidences were similar in all female groups. Because of the small size of the adrenal medulla, pheochromocytomas tend to obscure much or all of the remaining tissue. Therefore, the lower incidences of hyperplasia in groups of exposed males can be attributed, in part, to the larger number of pheochromocytomas.

While the increased incidences of pheochromocytomas in male rats were exposure related, it was believed to represent some, rather than clear, evidence of carcinogenic activity because a) the increase was associated primarily with benign neoplasms and b) there was no supporting increase in the incidence of hyperplasia. The increased incidence of pheochromocytomas in female rats was also exposure related.

Although the strength of the statistical association indicates that the pheochromocytomas are exposure related, a plausible mechanism for their increased occurrence in rats exposed to talc aerosols is not readily apparent. Since talc is relatively insoluble, it is extremely unlikely that any soluble components could have reached concentrations high enough in the blood to affect the adrenal medulla cells. Although purely speculative, there are two general hypotheses that might be considered. First, the increased incidence of adrenal pheochromocytomas may be a nonspecific effect of stress as a result of the chronic pulmonary inflammation. The body is known to respond to an exogenous challenge such as injury, inflammation, or infection by a set of distinct physiologic, metabolic, and endocrine changes including increases in serum adrenocorticotrophic hormone and cortisone levels, growth hormone, and catecholamine synthesis. Further, the adrenal medulla, as a modified sympathetic ganglia, reacts to neural as well as hormonal stimuli in the secretion of catecholamines. While prolonged stimulus of secretion is coupled with cellular hypertrophy and hyperplasia (cell proliferation) in many endocrine tissues, it is unknown if this occurs in the adrenal medulla. Moreover, if prolonged stress were to increase the rate of occurrence or growth of medullary proliferative lesions, similar exposure-related increases in pheochromocytoma incidence might be expected in other chronic toxicity and carcinogenicity studies. This has not generally been the case. Exposure-related increased incidences of pheochromocytoma were either not observed or not reported in the 2-year inhalation studies of other particulate substances reported above.

A second hypothesis to consider is that cytokines (growth factors), released from macrophages or other cells in the lung, might be responsible for increasing the rate of growth of pheochromocytomas. Although alveolar macrophages have been shown to secrete a number of cytokines known to stimulate proliferation of a variety of cell types, cytokines are generally believed to affect cells only in close proximity within the same organ. However, it has recently been shown that measurable levels of hepatocyte growth factor are present in the plasma after two-thirds hepatectomy (Lindroos *et al.*, 1992). Thus, some cytokines or growth factors may have wider effects than currently known.

CONCLUSIONS

Under the conditions of these inhalation studies, there was *some evidence of carcinogenic activity** of talc in male F344/N rats based on an increased incidence of benign and malignant pheochromocytomas of the adrenal gland. There was *clear evidence of carcinogenic activity* of talc in female F344/N rats based on increased incidences of alveolar/bronchiolar adenomas and carcinomas of

the lung and benign and malignant pheochromocytomas of the adrenal gland. There was *no evidence of carcinogenic activity* of talc in male or female $B6C3F_1$ mice exposed to 6 or 18 mg/m^3.

The principal toxic lesions associated with inhalation exposure to talc in rats included chronic granulomatous inflammation, alveolar epithelial hyperplasia, squamous metaplasia and squamous cysts, and interstitial fibrosis of the lung. These lesions were accompanied by impaired pulmonary function characterized primarily by reduced lung volumes, reduced dynamic and/or quasistatic lung compliance, reduced gas exchange efficiency, and nonuniform intrapulmonary gas distribution. In mice, inhalation exposure to talc produced chronic inflammation of the lung with the accumulation of alveolar macrophages.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE LIFETIME INHALATION STUDY OF TALC

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the Lifetime Inhalation Study of Talc[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Moribund	23	19	20
Natural deaths	18	17	14
Survivors			
Died last week of study	1	2	3
Terminal sacrifice	8	12	13
Animals examined microscopically	49	50	50
Alimentary System			
Intestine large, cecum	(42)	(38)	(37)
Intestine large, colon	(43)	(43)	(46)
Intestine small, duodenum	(48)	(44)	(46)
Intestine small, ileum	(39)	(34)	(35)
Intestine small, jejunum	(40)	(38)	(40)
Liver	(49)	(50)	(48)
Neoplastic nodule			1 (2%)
Neoplastic nodule, multiple	2 (4%)	1 (2%)	3 (6%)
Osteosarcoma, metastatic, multiple, bone	1 (2%)		
Hepatocyte, adenoma		1 (2%)	
Mesentery	(2)		(1)
Pancreas	(48)	(46)	(47)
Salivary glands	(49)	(50)	(50)
Fibroma		1 (2%)	
Stomach, forestomach	(49)	(47)	(47)
Fibrosarcoma			1 (2%)
Stomach, glandular	(49)	(47)	(47)
Fibrosarcoma			1 (2%)
Cardiovascular System			
Heart	(49)	(50)	(50)
Endocrine System			
Adrenal gland, cortex	(49)	(49)	(48)
Adrenal gland, medulla	(49)	(48)	(47)
Osteosarcoma, metastatic, uncertain primary site			1 (2%)
Pheochromocytoma malignant	2 (4%)	3 (6%)	6 (13%)
Pheochromocytoma complex		2 (4%)	1 (2%)
Pheochromocytoma benign	13 (27%)	9 (19%)	20 (43%)
Bilateral, pheochromocytoma malignant	1 (2%)		1 (2%)
Bilateral, pheochromocytoma benign	12 (24%)	21 (44%)	16 (34%)
Islets, pancreatic	(47)	(41)	(43)
Adenoma	1 (2%)		2 (5%)
Carcinoma	1 (2%)		
Parathyroid gland	(45)	(45)	(46)
Adenoma		1 (2%)	
Pituitary gland	(47)	(50)	(49)
Pars distalis, adenoma	12 (26%)	11 (22%)	10 (20%)
Pars distalis, carcinoma		1 (2%)	
Pars intermedia, adenoma			2 (4%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the Lifetime Inhalation Study of Talc (continued)

	0 mg/m^3	6 mg/m^3	18 mg/m^3
Endocrine System (continued)			
Thyroid gland	(45)	(46)	(46)
C-cell, adenoma	3 (7%)	4 (9%)	3 (7%)
C-cell, carcinoma		1 (2%)	
Follicular cell, adenoma			1 (2%)
General Body System			
Tissue NOS	(1)	(1)	
Pheochromocytoma malignant, metastatic, adrenal gland		1 (100%)	
Genital System			
Epididymis	(49)	(50)	(49)
Preputial gland	(48)	(49)	(48)
Adenoma	1 (2%)	1 (2%)	1 (2%)
Carcinoma	1 (2%)	6 (12%)	1 (2%)
Prostate	(49)	(45)	(48)
Seminal vesicle	(49)	(48)	(47)
Testes	(49)	(50)	(50)
Bilateral, interstitial cell, adenoma	18 (37%)	24 (48%)	24 (48%)
Interstitial cell, adenoma	13 (27%)	15 (30%)	12 (24%)
Hematopoietic System			
Bone marrow	(48)	(48)	(47)
Lymph node	(49)	(50)	(50)
Lymph node, bronchial	(41)	(48)	(49)
Lymph node, mandibular	(46)	(48)	(47)
Lymph node, mediastinal	(48)	(49)	(47)
Lymph node, mesenteric	(49)	(48)	(47)
Spleen	(49)	(50)	(48)
Fibrosarcoma	1 (2%)		
Fibrous histiocytoma		1 (2%)	
Osteosarcoma, metastatic, bone	1 (2%)		
Thymus	(48)	(40)	(43)
Thymoma malignant	1 (2%)		
Integumentary System			
Mammary gland	(45)	(48)	(50)
Adenocarcinoma	1 (2%)		
Skin	(48)	(50)	(50)
Basosquamous tumor malignant			1 (2%)
Fibroma		2 (4%)	
Fibrous histiocytoma			1 (2%)
Keratoacanthoma		2 (4%)	2 (4%)
Neurofibroma		1 (2%)	
Squamous cell carcinoma		1 (2%)	
Subcutaneous tissue, fibroma		1 (2%)	
Subcutaneous tissue, fibrosarcoma		1 (2%)	
Subcutaneous tissue, schwannoma malignant	1 (2%)		

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the Lifetime Inhalation Study of Talc (continued)

	0 mg/m³	6 mg/m³	18 mg/m³
Musculoskeletal System			
Bone	(49)	(50)	(50)
Pelvis, osteosarcoma		1 (2%)	
Scapula, osteosarcoma	1 (2%)		
Vertebra, osteosarcoma			1 (2%)
Skeletal muscle	(1)		
Nervous System			
Brain	(49)	(50)	(50)
Astrocytoma malignant	1 (2%)		
Respiratory System			
Lung	(49)	(50)	(50)
Alveolar/bronchiolar adenoma		1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma, multiple			1 (2%)
Fibrosarcoma, metastatic, salivary glands	1 (2%)		
Osteosarcoma, metastatic		1 (2%)	
Osteosarcoma, metastatic, uncertain primary site			1 (2%)
Osteosarcoma, metastatic, multiple, bone	1 (2%)		
Nose	(49)	(48)	(47)
Chondroma	1 (2%)		
Sarcoma		1 (2%)	
Special Senses System			
None			
Urinary System			
Kidney	(49)	(49)	(48)
Renal tubule, carcinoma	2 (4%)		
Urinary bladder	(49)	(48)	(47)
Papilloma	1 (2%)		
Systemic Lesions			
Multiple organs[b]	(49)	(50)	(50)
Leukemia mononuclear	24 (49%)	21 (42%)	23 (46%)
Lymphoma malignant lymphocytic	1 (2%)		
Mesothelioma benign	1 (2%)		
Mesothelioma malignant			1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the Lifetime Inhalation Study of Talc (continued)

	0 mg/m³	6 mg/m³	18 mg/m³
Tumor Summary			
Total animals with primary neoplasms[c]	48	49	50
Total primary neoplasms	116	135	137
Total animals with benign neoplasms	42	45	45
Total benign neoplasms	78	96	98
Total animals with malignant neoplasms	34	33	33
Total malignant neoplasms	38	39	39
Total animals with metastatic neoplasms	2	2	1
Total metastatic neoplasms	4	2	2
Total animals with malignant neoplasms, uncertain primary site			1

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.
[b] Number of animals with any tissue examined microscopically
[c] Primary tumors: all tumors except metastatic tumors

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Lifetime Inhalation Study of Talc: 0 mg/m³

Number of Days on Study	334	360	429	551	568	586	590	593	622	628	631	635	650	656	670	682	682	698	700	700	704	709	734	739
Carcass ID Number	3611	3081	3681	3401	4131	2941	2951	3881	3871	4201	3391	3421	3631	4181	3451	3431	3481	3171	3161	3851	3901	3131	2961	4141
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	M	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	M	+	+	+	+	+	+	+	+	M	+	+	+	A	M	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	A	+	A
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	A
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule, multiple																		X						
Osteosarcoma, metastatic, multiple, bone										X														
Mesentery	+								[illegible]															
Pancreas	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Blood vessel				+											+									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant															X									
Pheochromocytoma benign			X												X	X		X	X					
Bilateral, pheochromocytoma malignant																								
Bilateral, pheochromocytoma benign													X								X			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Carcinoma																								
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	I	+	+	+	+	+
Pars distalis, adenoma					X				X	X		X								X	X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																	X							

+: Tissue examined microscopically
A: Autolysis precludes examination

M: Missing tissue
I: Insufficient tissue

X: Lesion present
Blank: Not examined

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Lifetime Inhalation Study of Talc: 0 mg/m³ (continued)

Number of Days on Study	740	741	745	746	747	759	761	764	766	782	784	785	786	787	790	795	799	799	799	799	800	800	800	800	800	
Carcass ID Number	3671	2981	3621	2911	3191	4111	4101	3911	3471	3231	3981	3881	4151	3211	3961	3371	3241	3691	3711	3861	2931	2971	3221	3441	4191	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	A	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, cecum	+	A	+	+	+	+	M	A	+	+	A	+	A	+	+	+	+	+	+	A	+	+	+	+	+	42
Intestine large, colon	+	A	+	+	+	+	+	A	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large, rectum	M	+	+	M	+	+	+	A	+	+	A	M	A	M	+	+	+	+	+	+	+	+	+	+	+	38
Intestine small	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	A	+	+	+	+	+	A	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	39
Intestine small, jejunum	+	A	+	+	+	+	+	A	+	+	A	+	A	+	+	+	+	+	+	A	+	+	+	+	+	40
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule, multiple														X												2
Osteosarcoma, metastatic, multiple, bone																										1
Mesentery				+																						2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel								+												+						4
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant		X																								2
Pheochromocytoma benign		X					X		X	X				X					X					X	X	13
Bilateral, pheochromocytoma malignant																				X						1
Bilateral, pheochromocytoma benign				X	X	X		X			X				X	X		X				X	X			12
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	47
Adenoma																			X							1
Carcinoma																								X		1
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pars distalis, adenoma	X											X	X					X				X			X	12
Thyroid gland	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	M	+	+	+	+	+	+	+	+	+	45
C-cell, adenoma																		X					X			3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Lifetime Inhalation Study of Talc: 0 mg/m³ (continued)

Number of Days on Study	334	362	429	551	568	586	590	593	622	628	631	635	650	656	670	682	682	698	700	700	704	709	724	739
Carcass ID Number	3611	3001	3681	3401	4131	2941	2951	3181	3871	4201	3391	3421	3631	4181	3451	3431	3481	3171	3161	3851	3901	3131	2961	4141
General Body System																								
Tissue NOS			+																					
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X																					
Carcinoma						X																		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma													X			X							X	X
Interstitial cell, adenoma				X					X									X	X			X		
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma														X										
Osteosarcoma, metastatic, bone										X														
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma malignant		X																						
Integumentary System																								
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+
Adenocarcinoma																								
Skin	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, schwannoma malignant																					X			
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Scapula, osteosarcoma										X														
Skeletal muscle	+																							

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Lifetime Inhalation Study of Talc: 0 mg/m³ (continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	8	8	8	8	8	
	4	4	4	4	4	5	6	6	6	8	8	8	8	8	9	9	9	9	9	9	0	0	0	0	0	
	0	1	5	6	7	9	1	4	6	2	4	5	6	7	0	5	9	9	9	9	0	0	0	0	0	
Carcass ID Number	3	2	3	2	3	4	4	3	3	3	3	3	4	3	3	3	3	3	3	3	2	2	3	3	4	**Total**
	6	9	6	9	1	1	1	9	4	2	8	8	1	2	9	3	2	6	7	8	9	9	2	4	1	**Tissues/**
	7	8	2	1	9	1	0	1	7	3	9	8	5	1	6	7	4	9	1	6	3	7	2	4	9	**Tumors**
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
General Body System																										
Tissue NOS																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										1
Carcinoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, interstitial cell, adenoma		X	X			X	X	X	X	X	X					X	X		X		X	X			X	18
Interstitial cell, adenoma					X								X	X	X			X		X			X	X		13
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	M	I	+	+	M	+	+	+	M	+	+	+	+	M	M	41
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	46
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma																										1
Osteosarcoma, metastatic, bone																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymoma malignant																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenocarcinoma													X													1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Subcutaneous tissue, schwannoma malignant																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Scapula, osteosarcoma																										1
Skeletal muscle																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Lifetime Inhalation Study of Talc: 0 mg/m³ (continued)

Number of Days on Study	334	362	429	551	568	586	590	593	622	628	631	635	650	656	670	682	682	698	700	700	704	709	724	739
Carcass ID Number	3611	3081	3681	3401	4131	2941	2951	3181	3871	4201	3391	3421	3631	4181	3451	3431	3481	3171	3161	3851	3901	3131	2961	4141
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																								
Respiratory System																								
Larynx	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, salivary glands																					X			
Osteosarcoma, metastatic, multiple, bone										X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chondroma																	X							
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye														+									+	
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, carcinoma																								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma																								
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X			X				X	X		X	X	X			X		X	X		X	X	X	X
Lymphoma malignant lymphocytic																								
Mesothelioma benign					X																			

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Lifetime Inhalation Study of Talc: 0 mg/m³ (continued)

Number of Days on Study	740	741	745	746	747	759	761	764	766	782	784	785	786	787	790	795	799	799	799	799	800	800	800	800	800	
Carcass ID Number	3671	2981	3621	2911	3191	4111	4101	3911	3471	3231	3891	3881	4151	3211	3961	3371	3241	3691	3711	3861	2931	2971	3241	3441	4191	**Total Tissues/ Tumors**
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Astrocytoma malignant															X											1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma, metastatic, salivary glands																										1
Osteosarcoma, metastatic, multiple, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Chondroma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye											+															3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Renal tubule, carcinoma										X					X											2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma							X																			1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear	X		X	X	X		X			X					X				X		X		X			24
Lymphoma malignant lymphocytic																									X	1
Mesothelioma benign																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Lifetime Inhalation Study of Talc: 6 mg/m³

	1	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7
Number of Days on Study	8	2	2	4	5	7	9	9	0	1	3	4	5	5	6	7	7	9	1	2	2	3	3	4	4
	6	7	9	4	8	3	3	3	4	1	3	8	0	7	3	3	7	0	5	2	8	4	9	0	1
	0	0	1	0	1	0	0	1	0	0	0	1	0	0	0	1	0	0	1	0	0	0	0	0	1
Carcass ID Number	0	2	0	5	0	0	4	0	7	1	7	2	6	3	5	0	0	5	0	1	8	9	8	5	2
	6	9	7	9	5	4	9	3	3	1	9	8	0	1	7	0	3	3	2	2	3	7	4	6	4
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	A	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+
Intestine large, cecum	+	+	+	A	+	+	+	+	+	A	A	A	+	+	A	+	+	+	+	A	+	+	+	+	A
Intestine large, colon	+	+	+	A	+	+	+	+	+	+	A	A	+	+	A	+	+	+	+	A	+	+	+	+	+
Intestine large, rectum	+	+	+	A	+	M	+	+	M	+	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+
Intestine small	+	+	+	A	+	+	+	+	+	+	A	A	+	+	A	+	+	+	+	A	+	+	+	+	+
Intestine small, duodenum	+	+	+	A	+	+	+	+	+	+	A	A	+	+	A	+	+	+	+	A	+	+	+	+	+
Intestine small, ileum	+	+	+	A	+	+	+	+	+	A	A	A	+	+	A	+	+	+	A	A	+	+	+	A	A
Intestine small, jejunum	+	+	+	A	+	+	+	+	+	A	A	A	+	+	A	+	+	+	A	A	+	+	+	+	A
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule, multiple																									
Hepatocyte, adenoma																									
Pancreas	+	+	+	A	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	A	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Stomach	+	+	+	A	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	A	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	A	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel									+													+			
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	A	+	+	I	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant				X																					
Pheochromocytoma complex					X																				
Pheochromocytoma benign					X							X				X	X				X				
Bilateral, pheochromocytoma benign							X		X											X		X		X	
Islets, pancreatic	+	+	+	A	+	+	+	+	+	+	A	A	+	+	+	M	+	+	+	A	+	+	M	+	+
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X											X					X		X		
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	A	+	+	+	+	+	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Lifetime Inhalation Study of Talc: 6 mg/m³ (continued)

Number of Days on Study	746	747	757	759	761	762	780	781	783	787	791	799	799	799	799	799	799	799	800	800	800	800	800	800	800	
Carcass ID Number	0261	1321	0981	0321	1261	1041	0511	0501	0281	0051	0341	0011	0301	0351	0361	0521	0741	0751	0081	0781	0991	1211	1251	1291	1301	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, cecum	+	+	A	A	+	A	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	38
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	43
Intestine large, rectum	+	+	M	M	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Intestine small	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, ileum	+	A	A	A	+	A	+	+	A	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	34
Intestine small, jejunum	+	+	+	A	+	+	+	+	A	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	38
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule, multiple												X														1
Hepatocyte, adenoma																									X	1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma									X																	1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Cardiovascular System																										
Blood vessel			+					+	+																	5
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma malignant											X		X													3
Pheochromocytoma complex																							X			2
Pheochromocytoma benign											X						X					X	X			9
Bilateral, pheochromocytoma benign	X		X	X		X	X	X	X	X				X	X	X		X		X	X			X	X	21
Islets, pancreatic	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	41
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma																										1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X			X		X					X	X						X						11
Pars distalis, carcinoma							X																			1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
C-cell, adenoma												X		X					X		X					4
C-cell, carcinoma										X																1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Lifetime Inhalation Study of Talc: 6 mg/m³ (continued)

Number of Days on Study	1	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7
	8	2	2	4	5	7	9	9	0	1	3	4	5	5	6	7	7	9	1	2	2	3	3	4	4
	6	7	9	4	8	3	3	3	4	1	3	8	0	7	3	3	7	0	5	2	8	4	9	0	1
Carcass ID Number	0	0	1	0	1	0	0	1	0	0	0	1	0	0	0	1	0	0	1	0	0	0	0	0	1
	0	2	0	5	0	0	4	0	7	1	7	2	6	3	5	0	0	5	0	1	8	9	8	5	2
	6	9	7	9	5	4	9	3	3	1	9	8	0	1	7	0	3	3	2	2	3	7	4	6	4
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
General Body System																									
Tissue NOS																					+				
Pheochromocytoma malignant, metastatic, adrenal gland																					X				
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma		X			X																		X	X	
Prostate	+	+	+	M	+	+	+	+	M	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	A
Seminal vesicle	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma									X			X	X				X		X	X			X		X
Interstitial cell, adenoma				X		X				X					X			X				X			
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	I	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma																									
Thymus	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	I	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma														X											
Keratoacanthoma															X										
Neurofibroma																									
Squamous cell carcinoma																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Lifetime Inhalation Study of Talc: 6 mg/m³ (continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	8	8	8	8	8	8	8	
	4	4	5	5	6	6	8	8	8	8	9	9	9	9	9	9	9	9	0	0	0	0	0	0	0	
	6	7	7	9	1	2	0	1	3	7	1	9	9	9	9	9	9	9	0	0	0	0	0	0	0	
Carcass ID Number	0	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	
	2	3	9	3	2	0	5	5	2	0	3	0	3	3	3	5	7	7	0	7	9	2	2	2	3	**Total**
	6	2	8	2	6	4	1	0	8	5	4	1	0	5	6	2	4	5	8	8	9	1	5	9	0	**Tissues/**
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	**Tumors**
General Body System																										
Tissue NOS																										1
Pheochromocytoma malignant, metastatic, adrenal gland																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																							X			1
Carcinoma										X										X						6
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X						X	X		X			X	X	X	X		X	X	X	X	X	X	24
Interstitial cell, adenoma				X	X	X	X	X			X		X	X					X							15
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma												X														1
Thymus	+	M	+	+	+	+	+	+	+	M	I	+	+	+	M	+	+	+	+	+	+	M	+	M	+	40
Integumentary System																										
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma																							X			2
Keratoacanthoma																					X					2
Neurofibroma							X																			1
Squamous cell carcinoma		X																								1
Subcutaneous tissue, fibroma																		X								1
Subcutaneous tissue, fibrosarcoma			X																							1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Lifetime Inhalation Study of Talc: 6 mg/m^3 (continued)

Number of Days on Study	1	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7
	8	2	2	4	5	7	9	9	0	1	3	4	5	5	6	7	7	9	1	2	2	3	3	4	4
	6	7	9	4	8	3	3	3	4	1	3	8	0	7	3	3	7	0	5	2	8	4	9	0	1
Carcass ID Number	0	0	1	0	1	0	0	1	0	0	0	1	0	0	0	1	0	0	1	0	0	0	0	0	1
	0	2	0	5	0	0	4	0	7	1	7	2	6	3	5	0	0	5	0	1	8	9	8	5	2
	6	9	7	9	5	4	9	3	3	1	9	8	0	1	7	0	3	3	2	2	3	7	4	6	4
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pelvis, osteosarcoma										X															
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Osteosarcoma, metastatic										X															
Nose	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma															X										
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+																								
Urinary System																									
Kidney	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X		X	X	X			X	X	X				X	X					X		X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Lifetime Inhalation Study of Talc: 6 mg/m³ (continued)

Number of Days on Study	746	747	757	759	761	762	780	781	783	787	791	799	799	799	799	799	799	799	800	800	800	800	800	800	800	
Carcass ID Number	0261	1321	0981	0321	1261	1041	0511	0501	0281	0051	0341	0011	0301	0351	0361	0521	0741	0751	0081	0781	0991	1211	1251	1291	1301	**Total Tissues/ Tumors**
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pelvis, osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X																		1
Osteosarcoma, metastatic																										1
Nose	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Sarcoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																					+					2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X			X	X		X		X						X			X		X				X		21

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Lifetime Inhalation Study of Talc: 18 mg/m³

Number of Days on Study	248	492	500	594	607	609	614	615	615	617	628	634	645	651	651	653	676	683	697	698	701	705	719	722	737
Carcass ID Number	2191	1451	2031	1771	2441	1741	1751	1491	2241	2661	1951	2171	2511	2021	2271	2671	2701	2261	1761	1521	2251	1511	2521	1501	1721
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	A	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	A	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	M	M	A	+	+	+	+	+	+	M	+	A	+	+	+	+	+	M	M	M	M	+	M	+
Intestine small	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	M	A	A	A	+	+	+	+	M	+	+	+	A	+	+	+	+	+	+	A	A	A	+	+	+
Intestine small, jejunum	+	A	A	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	A	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																						X			
Neoplastic nodule, multiple									X															X	
Mesentery																							+		
Pancreas	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma			X																						
Stomach, glandular	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma			X																						
Tongue																									
Cardiovascular System																									
Blood vessel				+									+								+				
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, uncertain primary site																							X		
Pheochromocytoma malignant													X												
Pheochromocytoma complex																									
Pheochromocytoma benign									X	X	X	X	X	X			X		X						
Bilateral, pheochromocytoma malignant																									
Bilateral, pheochromocytoma benign							X														X	X		X	X
Islets, pancreatic	+	+	+	A	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X															
Parathyroid gland	M	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																			X	X			X		
Pars intermedia, adenoma										X		X													
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
C-cell, adenoma							X																		
Follicular cell, adenoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Lifetime Inhalation Study of Talc: 18 mg/m^3 (continued)

Number of Days on Study	743	778	783	788	791	791	793	794	798	799	799	799	799	799	799	799	799	800	800	800	800	800	800	800	800	
Carcass ID Number	2221	2011	2421	1941	2451	2741	2711	1971	1461	1551	1561	1691	1781	1801	1931	1961	1981	2201	2281	2431	2461	2471	2681	2751	2761	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	49
Intestine large	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	A	A	+	+	A	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	37
Intestine large, colon	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	46
Intestine large, rectum	A	A	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	34
Intestine small	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	A	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	35
Intestine small, jejunum	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	40
Liver	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Neoplastic nodule																										1
Neoplastic nodule, multiple																								X		3
Mesentery																										1
Pancreas	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, forestomach	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Fibrosarcoma																										1
Stomach, glandular	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Fibrosarcoma																										1
Tongue					+																					1
Cardiovascular System																										
Blood vessel			+														+									5
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal gland, medulla	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Osteosarcoma, metastatic, uncertain primary site																										1
Pheochromocytoma malignant			X		X											X			X	X						6
Pheochromocytoma complex	X																									1
Pheochromocytoma benign	X		X		X					X		X			X	X			X	X	X	X	X			20
Bilateral, pheochromocytoma malignant						X																				1
Bilateral, pheochromocytoma benign				X			X	X	X		X		X	X			X	X						X	X	16
Islets, pancreatic	A	A	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	43
Adenoma																								X		2
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma				X			X	X		X							X	X				X				10
Pars intermedia, adenoma																										2
Thyroid gland	A	A	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
C-cell, adenoma										X									X							3
Follicular cell, adenoma																			X							1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Lifetime Inhalation Study of Talc: 18 mg/m³ (continued)

Number of Days on Study	2	4	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7
	4	9	0	9	0	0	1	1	1	1	2	3	4	5	5	5	7	8	9	9	0	0	1	2	3
	8	2	0	4	7	9	4	5	5	7	8	4	5	1	1	3	6	3	7	8	1	5	9	2	7
Carcass ID Number	2	1	2	1	2	1	1	1	2	2	1	2	2	2	2	2	2	2	1	1	2	1	2	1	1
	1	4	0	7	4	7	7	4	2	6	9	1	5	0	2	6	7	2	7	5	2	5	5	5	7
	9	5	3	7	4	4	5	9	4	6	5	7	1	2	7	7	0	6	6	2	5	1	2	0	2
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																									
Preputial gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Adenoma											X														
Carcinoma																									
Prostate	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma											X				X	X	X				X	X	X		X
Interstitial cell, adenoma						X	X			X		X		X				X						X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	A	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	I	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	I	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor malignant														X											
Fibrous histiocytoma																									
Keratoacanthoma				X																					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vertebra, osteosarcoma	X																								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Lifetime Inhalation Study of Talc: 18 mg/m³ (continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	8	8	8	8	8	8	8	8	
	4	7	8	8	9	9	9	9	9	9	9	9	9	9	9	9	9	0	0	0	0	0	0	0	0	
	3	8	3	8	1	1	3	4	8	9	9	9	9	9	9	9	9	0	0	0	0	0	0	0	0	
Carcass ID Number	2	2	2	1	2	2	2	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	**Total**
	2	0	4	9	4	7	7	9	4	5	5	6	7	8	9	9	9	2	2	4	4	4	6	7	7	**Tissues/**
	2	1	2	4	5	4	1	7	6	5	6	9	8	0	3	6	8	0	8	3	6	7	8	5	6	**Tumors**
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Penis												+			+					+						3
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma														X												1
Carcinoma																										1
Prostate	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Seminal vesicle	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X		X		X			X			X		X	X		X	X	X		X	X	X	X	X	24
Interstitial cell, adenoma					X						X		X			X				X						12
Hematopoietic System																										
Bone marrow	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mandibular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	47
Lymph node, mesenteric	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	A	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	43
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basosquamous tumor malignant																										1
Fibrous histiocytoma														X												1
Keratoacanthoma				X																						2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Vertebra, osteosarcoma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Lifetime Inhalation Study of Talc: 18 mg/m^3 (continued)

Number of Days on Study	2	4	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7
	4	9	0	9	0	0	1	1	1	1	2	3	4	5	5	5	7	8	9	9	0	0	1	2	3
	8	2	0	4	7	9	4	5	5	7	8	4	5	1	1	3	6	3	7	8	1	5	9	2	7
Carcass ID Number	2	1	2	1	2	1	1	1	2	2	1	2	2	2	2	2	2	2	1	1	2	1	2	1	1
	1	4	0	7	4	7	7	4	2	6	9	1	5	0	2	6	7	2	7	5	2	5	5	5	7
	9	5	3	7	4	4	5	9	4	6	5	7	1	2	7	7	0	6	6	2	5	1	2	0	2
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+																								
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma, multiple																									
Osteosarcoma, metastatic, uncertain primary site																							X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye												+												+	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter																							+		
Urethra																									
Urinary bladder	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X			X	X	X	X	X	X				X	X	X	X			X		X		X	
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the Lifetime Inhalation Study of Talc: 18 mg/m³ (continued)

Number of Days on Study	743	778	783	788	791	791	793	794	798	799	799	799	799	799	799	799	799	800	800	800	800	800	800	800	800	
Carcass ID Number	2221	2011	2421	1941	2451	2741	2711	1971	1461	1551	1561	1691	1781	1801	1931	1961	1981	2201	2281	2431	2461	2471	2681	2751	2761	**Total Tissues/ Tumors**
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1
Respiratory System																										
Larynx	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma													X													1
Alveolar/bronchiolar carcinoma, multiple													X													1
Osteosarcoma, metastatic, uncertain primary site																										1
Nose	A	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Trachea	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Special Senses System																										
Eye																										2
Urinary System																										
Kidney	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Ureter																										1
Urethra												+														1
Urinary bladder	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X		X						X		X	X		X					X				X		23
Mesothelioma malignant						X																				1

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the Lifetime Inhalation Study of Talc

	0 mg/m^3	6 mg/m^3	18 mg/m^3
Adrenal Medulla: Benign Pheochromocytoma			
Overall rates[a]	25/49 (51%)	30/48 (63%)	36/47 (77%)
Adjusted rates[b]	87.6%	90.2%	100.0%
Terminal rates[c]	6/9 (67%)	11/14 (79%)	16/16 (100%)
First incidence (days)	429	558	614
Life table tests[d]	P=0.434	P=0.515N	P=0.499
Logistic regression tests[d]	P=0.007	P=0.213	P=0.009
Cochran-Armitage test[d]	P=0.007		
Fisher exact test[d]		P=0.175	P=0.008
Adrenal Medulla: Malignant Pheochromocytoma			
Overall rates	3/49 (6%)	3/48 (6%)	7/47 (15%)
Adjusted rates	17.2%	15.2%	31.5%
Terminal rates	1/9 (11%)	1/14 (7%)	3/16 (19%)
First incidence (days)	670	544	645
Life table tests	P=0.242	P=0.552N	P=0.376
Logistic regression tests	P=0.096	P=0.662	P=0.178
Cochran-Armitage test	P=0.083		
Fisher exact test		P=0.651	P=0.142
Adrenal Medulla: Benign, Malignant, or Complex Pheochromocytoma			
Overall rates	26/49 (53%)	32/48 (67%)	37/47 (79%)
Adjusted rates	91.7%	93.6%	100.0%
Terminal rates	7/9 (78%)	12/14 (86%)	16/16 (100%)
First incidence (days)	429	544	614
Life table tests	P=0.483	P=0.549N	P=0.539
Logistic regression tests	P=0.007	P=0.147	P=0.006
Cochran-Armitage test	P=0.007		
Fisher exact test		P=0.123	P=0.007
Liver: Hepatocellular Adenoma or Neoplastic Nodule			
Overall rates	2/49 (4%)	2/50 (4%)	4/48 (8%)
Adjusted rates	11.2%	14.3%	14.9%
Terminal rates	0/9 (0%)	2/14 (14%)	1/16 (6%)
First incidence (days)	698	799 (T)	615
Life table tests	P=0.359	P=0.586N	P=0.434
Logistic regression tests	P=0.248	P=0.661N	P=0.333
Cochran-Armitage test	P=0.237		
Fisher exact test		P=0.684N	P=0.329
Pancreatic Islets: Adenoma			
Overall rates	1/47 (2%)	0/41 (0%)	2/43 (5%)
Adjusted rates	12.5%	0.0%	9.9%
Terminal rates	1/8 (13%)	0/13 (0%)	1/13 (8%)
First incidence (days)	799 (T)	–[e]	617
Life table tests	P=0.387	P=0.403N	P=0.612
Logistic regression tests	P=0.308	P=0.403N	P=0.479
Cochran-Armitage test	P=0.304		
Fisher exact test		P=0.534N	P=0.466

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the Lifetime Inhalation Study of Talc (continued)

	0 mg/m^3	6 mg/m^3	18 mg/m^3
Pancreatic Islets: Adenoma or Carcinoma			
Overall rates	2/47 (4%)	0/41 (0%)	2/43 (5%)
Adjusted rates	25.0%	0.0%	9.9%
Terminal rates	2/8 (25%)	0/13 (0%)	1/13 (8%)
First incidence (days)	799 (T)	–	617
Life table tests	P=0.650	P=0.135N	P=0.560N
Logistic regression tests	P=0.544	P=0.135N	P=0.683
Cochran-Armitage test	P=0.531		
Fisher exact test		P=0.282N	P=0.657
Pituitary Gland (Pars Distalis): Adenoma			
Overall rates	12/47 (26%)	11/50 (22%)	10/49 (20%)
Adjusted rates	53.6%	42.8%	42.1%
Terminal rates	3/9 (33%)	3/14 (21%)	4/16 (25%)
First incidence (days)	568	558	697
Life table tests	P=0.174N	P=0.334N	P=0.160N
Logistic regression tests	P=0.307N	P=0.419N	P=0.324N
Cochran-Armitage test	P=0.344N		
Fisher exact test		P=0.432N	P=0.362N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma			
Overall rates	12/47 (26%)	12/50 (24%)	10/49 (20%)
Adjusted rates	53.6%	45.8%	42.1%
Terminal rates	3/9 (33%)	3/14 (21%)	4/16 (25%)
First incidence (days)	568	558	697
Life table tests	P=0.159N	P=0.411N	P=0.160N
Logistic regression tests	P=0.287N	P=0.509N	P=0.324N
Cochran-Armitage test	P=0.325N		
Fisher exact test		P=0.524N	P=0.362N
Preputial Gland: Carcinoma			
Overall rates	1/48 (2%)	6/49 (12%)	1/48 (2%)
Adjusted rates	2.3%	22.5%	2.5%
Terminal rates	0/9 (0%)	1/14 (7%)	0/16 (0%)
First incidence (days)	586	527	628
Life table tests	P=0.361N	P=0.090	P=0.753N
Logistic regression tests	P=0.440N	P=0.058	P=0.750
Cochran-Armitage test	P=0.425N		
Fisher exact test		P=0.059	P=0.753N
Preputial Gland: Adenoma or Carcinoma			
Overall rates	2/48 (4%)	7/49 (14%)	2/48 (4%)
Adjusted rates	4.4%	28.5%	8.6%
Terminal rates	0/9 (0%)	2/14 (14%)	1/16 (6%)
First incidence (days)	429	527	628
Life table tests	P=0.331N	P=0.134	P=0.632N
Logistic regression tests	P=0.454N	P=0.078	P=0.673
Cochran-Armitage test	P=0.436N		
Fisher exact test		P=0.084	P=0.692N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the Lifetime Inhalation Study of Talc (continued)

	0 mg/m³	6 mg/m³	18 mg/m³
Skin: Keratoacanthoma or Squamous Cell Carcinoma			
Overall rates	0/49 (0%)	3/50 (6%)	2/50 (4%)
Adjusted rates	0.0%	13.5%	6.6%
Terminal rates	0/9 (0%)	1/14 (7%)	0/16 (0%)
First incidence (days)	–	663	594
Life table tests	P=0.414	P=0.161	P=0.331
Logistic regression tests	P=0.323	P=0.128	P=0.239
Cochran-Armitage test	P=0.319		
Fisher exact test		P=0.125	P=0.253
Testes: Adenoma			
Overall rates	31/49 (63%)	39/50 (78%)	36/50 (72%)
Adjusted rates	100.0%	100.0%	97.0%
Terminal rates	9/9 (100%)	14/14 (100%)	15/16 (94%)
First incidence (days)	551	544	609
Life table tests	P=0.198N	P=0.524	P=0.245N
Logistic regression tests	P=0.333	P=0.056	P=0.268
Cochran-Armitage test	P=0.295		
Fisher exact test		P=0.082	P=0.238
Thyroid Gland (C-cell): Adenoma			
Overall rates	3/45 (7%)	4/46 (9%)	3/46 (7%)
Adjusted rates	24.5%	28.6%	14.5%
Terminal rates	2/9 (22%)	4/14 (29%)	2/16 (13%)
First incidence (days)	682	799 (T)	614
Life table tests	P=0.348N	P=0.620N	P=0.476N
Logistic regression tests	P=0.511N	P=0.641	P=0.625N
Cochran-Armitage test	P=0.560N		
Fisher exact test		P=0.512	P=0.651N
Thyroid Gland (C-cell): Adenoma or Carcinoma			
Overall rates	3/45 (7%)	5/46 (11%)	3/46 (7%)
Adjusted rates	24.5%	33.0%	14.5%
Terminal rates	2/9 (22%)	4/14 (29%)	2/16 (13%)
First incidence (days)	682	787	614
Life table tests	P=0.296N	P=0.568	P=0.476N
Logistic regression tests	P=0.467N	P=0.502	P=0.625N
Cochran-Armitage test	P=0.523N		
Fisher exact test		P=0.369	P=0.651N
All Organs: Mononuclear Cell Leukemia			
Overall rates	24/49 (49%)	21/50 (42%)	23/50 (46%)
Adjusted rates	70.3%	59.9%	62.5%
Terminal rates	3/9 (33%)	4/14 (29%)	6/16 (38%)
First incidence (days)	334	529	492
Life table tests	P=0.298N	P=0.232N	P=0.269N
Logistic regression tests	P=0.501N	P=0.317N	P=0.479N
Cochran-Armitage test	P=0.486N		
Fisher exact test		P=0.310N	P=0.462N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the Lifetime Inhalation Study of Talc (continued)

	0 mg/m³	6 mg/m³	18 mg/m³
All Organs: Benign Tumors			
Overall rates	42/49 (86%)	45/50 (90%)	45/50 (90%)
Adjusted rates	100.0%	100.0%	100.0%
Terminal rates	9/9 (100%)	14/14 (100%)	16/16 (100%)
First incidence (days)	429	544	594
Life table tests	P=0.161N	P=0.314N	P=0.153N
Logistic regression tests	P=0.463	P=0.430	P=0.480
Cochran-Armitage test	P=0.353		
Fisher exact test		P=0.365	P=0.365
All Organs: Malignant Tumors			
Overall rates	34/49 (69%)	34/50 (68%)	34/50 (68%)
Adjusted rates	88.4%	80.9%	80.0%
Terminal rates	6/9 (67%)	7/14 (50%)	9/16 (56%)
First incidence (days)	334	527	248
Life table tests	P=0.222N	P=0.308N	P=0.216N
Logistic regression tests	P=0.534N	P=0.539N	P=0.571N
Cochran-Armitage test	P=0.505N		
Fisher exact test		P=0.527N	P=0.527N
All Organs: Benign or Malignant Tumors			
Overall rates	48/49 (98%)	49/50 (98%)	50/50 (100%)
Adjusted rates	100.0%	100.0%	100.0%
Terminal rates	9/9 (100%)	14/14 (100%)	16/16 (100%)
First incidence (days)	334	527	248
Life table tests	P=0.154N	P=0.241N	P=0.139N
Logistic regression tests	P=0.337	P=0.771	P=0.506
Cochran-Armitage test	P=0.348		
Fisher exact test		P=0.747	P=0.495

(T)Terminal sacrifice

a Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.

b Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality

c Observed incidence at terminal kill

d Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.

e Not applicable; no tumors in animal group

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Lifetime Inhalation Study of Talc[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Moribund	23	19	20
Natural deaths	18	17	14
Survivors			
Died last week of study	1	2	3
Terminal sacrifice	8	12	13
Animals examined microscopically	49	50	50
Alimentary System			
Esophagus	(49)	(50)	(49)
Inflammation			1 (2%)
Intestine large, cecum	(42)	(38)	(37)
Hemorrhage		1 (3%)	
Inflammation	9 (21%)	2 (5%)	5 (14%)
Parasite metazoan	3 (7%)	4 (11%)	4 (11%)
Ulcer	1 (2%)		
Intestine large, colon	(43)	(43)	(46)
Hyperplasia, lymphoid	1 (2%)		
Inflammation	1 (2%)		1 (2%)
Mineralization			1 (2%)
Parasite metazoan	2 (5%)	1 (2%)	1 (2%)
Intestine large, rectum	(38)	(41)	(34)
Inflammation	6 (16%)	1 (2%)	1 (3%)
Metaplasia, squamous, focal			1 (3%)
Parasite metazoan		2 (5%)	
Intestine small, duodenum	(48)	(44)	(46)
Inflammation			1 (2%)
Mineralization	1 (2%)		
Necrosis, focal	1 (2%)		
Ulcer	1 (2%)	1 (2%)	
Intestine small, ileum	(39)	(34)	(35)
Hyperplasia, lymphoid		1 (3%)	2 (6%)
Lymphatic, ectasia		1 (3%)	
Liver	(49)	(50)	(48)
Angiectasis, focal	1 (2%)		
Atrophy	1 (2%)		
Basophilic focus	18 (37%)	18 (36%)	19 (40%)
Clear cell focus	3 (6%)	7 (14%)	4 (8%)
Congestion		1 (2%)	
Degeneration, cystic	9 (18%)	17 (34%)	9 (19%)
Degeneration, diffuse			1 (2%)
Eosinophilic focus	2 (4%)	7 (14%)	7 (15%)
Fatty change	16 (33%)	14 (28%)	12 (25%)
Fibrosis	1 (2%)		
Hematocyst		1 (2%)	
Hyperplasia, focal			1 (2%)
Inflammation, granulomatous, focal	3 (6%)	1 (2%)	
Inflammation, necrotizing, focal			1 (2%)
Necrosis, focal	3 (6%)		1 (2%)
Thrombosis	1 (2%)		
Bile duct, hyperplasia	39 (80%)	46 (92%)	44 (92%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Lifetime Inhalation Study of Talc (continued)

	0 mg/m³	6 mg/m³	18 mg/m³
Alimentary System (continued)			
Liver (continued)			
Centrilobular, atrophy	9 (18%)	4 (8%)	7 (15%)
Centrilobular, degeneration	8 (16%)	12 (24%)	9 (19%)
Centrilobular, degeneration, fatty			1 (2%)
Centrilobular, necrosis	5 (10%)		2 (4%)
Mesentery	(2)		(1)
Inflammation			1 (100%)
Pancreas	(48)	(46)	(47)
Lobules, atrophy	11 (23%)	7 (15%)	8 (17%)
Salivary glands	(49)	(50)	(50)
Inflammation	1 (2%)		
Necrosis			1 (2%)
Stomach, forestomach	(49)	(47)	(47)
Hyperkeratosis			1 (2%)
Inflammation	1 (2%)		
Mineralization	1 (2%)	4 (9%)	1 (2%)
Ulcer	5 (10%)	5 (11%)	8 (17%)
Stomach, glandular	(49)	(47)	(47)
Mineralization	6 (12%)	6 (13%)	6 (13%)
Ulcer	3 (6%)	3 (6%)	2 (4%)
Cardiovascular System			
Blood vessel	(4)	(5)	(5)
Aorta, mineralization	3 (75%)	5 (100%)	4 (80%)
Mesenteric artery, aneurysm			2 (40%)
Mesenteric artery, inflammation			1 (20%)
Mesenteric artery, mineralization	3 (75%)	5 (100%)	3 (60%)
Mesenteric artery, thrombosis	1 (25%)	1 (20%)	1 (20%)
Heart	(49)	(50)	(50)
Cardiomyopathy	42 (86%)	47 (94%)	50 (100%)
Atrium, thrombosis	9 (18%)	5 (10%)	11 (22%)
Epicardium, hyperplasia	1 (2%)		
Myocardium, inflammation		1 (2%)	
Myocardium, mineralization	2 (4%)	6 (12%)	5 (10%)
Endocrine System			
Adrenal gland, cortex	(49)	(49)	(48)
Degeneration	1 (2%)		
Degeneration, fatty	8 (16%)		2 (4%)
Degeneration, focal	1 (2%)		
Hyperplasia, diffuse			2 (4%)
Hyperplasia, focal	11 (22%)	4 (8%)	9 (19%)
Necrosis, focal	1 (2%)		
Adrenal gland, medulla	(49)	(48)	(47)
Hyperplasia	19 (39%)	8 (17%)	8 (17%)
Bilateral, hyperplasia	1 (2%)		1 (2%)
Islets, pancreatic	(47)	(41)	(43)
Hyperplasia			1 (2%)
Parathyroid gland	(45)	(45)	(46)
Hyperplasia	6 (13%)	11 (24%)	12 (26%)
Bilateral, hyperplasia	1 (2%)		

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Lifetime Inhalation Study of Talc (continued)

	0 mg/m^3	6 mg/m^3	18 mg/m^3
Endocrine System (continued)			
Pituitary gland	(47)	(50)	(49)
Angiectasis, focal		1 (2%)	
Cyst		1 (2%)	1 (2%)
Pars distalis, hyperplasia	8 (17%)	8 (16%)	7 (14%)
Pars nervosa, hyperplasia		1 (2%)	
Thyroid gland	(45)	(46)	(46)
C-cell, hyperplasia	5 (11%)	7 (15%)	2 (4%)
General Body System			
None			
Genital System			
Epididymis	(49)	(50)	(49)
Spermatocele		1 (2%)	
Preputial gland	(48)	(49)	(48)
Hyperplasia	3 (6%)		1 (2%)
Inflammation	7 (15%)	2 (4%)	5 (10%)
Prostate	(49)	(45)	(48)
Atrophy	1 (2%)		1 (2%)
Inflammation	22 (45%)	14 (31%)	19 (40%)
Seminal vesicle	(49)	(48)	(47)
Atrophy	1 (2%)		
Inflammation	1 (2%)		
Testes	(49)	(50)	(50)
Atrophy	14 (29%)	11 (22%)	16 (32%)
Hyperplasia, lymphoid		2 (4%)	
Hyperplasia, lymphoid, focal			1 (2%)
Interstitial cell, hyperplasia	2 (4%)	1 (2%)	3 (6%)
Serosa, proliferation			1 (2%)
Hematopoietic System			
Bone marrow	(48)	(48)	(47)
Atrophy			2 (4%)
Atrophy, focal		1 (2%)	
Inflammation		1 (2%)	
Myelofibrosis		1 (2%)	1 (2%)
Myeloid cell, hyperplasia	2 (4%)	3 (6%)	6 (13%)
Lymph node	(49)	(50)	(50)
Hemorrhage, chronic		1 (2%)	
Pancreatic, atrophy	1 (2%)		
Pancreatic, hyperplasia, lymphoid	1 (2%)		
Lymph node, bronchial	(41)	(48)	(49)
Atrophy	2 (5%)		
Hemorrhage		1 (2%)	
Hemorrhage, acute	1 (2%)		
Hemorrhage, chronic	4 (10%)		
Hyperplasia, histiocytic		44 (92%)	46 (94%)
Lymph node, mandibular	(46)	(48)	(47)
Hemorrhage		1 (2%)	
Hyperplasia, lymphoid		2 (4%)	
Hyperplasia, plasma cell		2 (4%)	5 (11%)
Inflammation, chronic active			2 (4%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Lifetime Inhalation Study of Talc (continued)

	0 mg/m^3	6 mg/m^3	18 mg/m^3
Hematopoietic System (continued)			
Lymph node, mediastinal	(48)	(49)	(47)
Atrophy	1 (2%)		
Hemorrhage		3 (6%)	
Hemorrhage, acute	1 (2%)		
Hemorrhage, chronic	6 (13%)		
Hyperplasia, histiocytic		40 (82%)	43 (91%)
Pigmentation, hemosiderin	1 (2%)		
Lymph node, mesenteric	(49)	(48)	(47)
Atrophy	1 (2%)		
Hemorrhage		2 (4%)	
Hemorrhage, acute	1 (2%)		
Hyperplasia, lymphoid	1 (2%)	2 (4%)	3 (6%)
Hyperplasia, plasma cell			1 (2%)
Inflammation, chronic active			1 (2%)
Spleen	(49)	(50)	(48)
Atrophy	1 (2%)		2 (4%)
Autolysis			1 (2%)
Congestion, chronic	1 (2%)		
Cyst			1 (2%)
Fibrosis		1 (2%)	
Fibrosis, focal		5 (10%)	2 (4%)
Hematopoietic cell proliferation	1 (2%)	2 (4%)	3 (6%)
Hyperplasia, histiocytic		1 (2%)	
Hyperplasia, lymphoid		1 (2%)	1 (2%)
Infarct	3 (6%)		
Inflammation, granulomatous, focal	1 (2%)		1 (2%)
Thymus	(48)	(40)	(43)
Atrophy		2 (5%)	
Cyst	1 (2%)		
Integumentary System			
Mammary gland	(45)	(48)	(50)
Galactocele	1 (2%)		
Skin	(48)	(50)	(50)
Cyst epithelial inclusion		1 (2%)	
Subcutaneous tissue, inflammation			1 (2%)
Tail, necrosis	1 (2%)		
Musculoskeletal System			
Bone	(49)	(50)	(50)
Fibrous osteodystrophy	3 (6%)	4 (8%)	5 (10%)
Coccygeal, necrosis	1 (2%)		
Pelvis, fracture		1 (2%)	
Nervous System			
Brain	(49)	(50)	(50)
Compression	5 (10%)	2 (4%)	2 (4%)
Hemorrhage		1 (2%)	
Infarct			1 (2%)
Necrosis, focal	1 (2%)	2 (4%)	
Spinal cord			(1)
Degeneration			1 (100%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Lifetime Inhalation Study of Talc (continued)

	0 mg/m^3	6 mg/m^3	18 mg/m^3
Respiratory System			
Larynx	(48)	(49)	(49)
Inflammation, suppurative	6 (13%)		
Lung	(49)	(50)	(50)
Congestion	1 (2%)		
Crystals, focal	1 (2%)		
Cyst			3 (6%)
Hemorrhage, chronic	2 (4%)		
Infarct	1 (2%)		
Inflammation, granulomatous	2 (4%)	50 (100%)	49 (98%)
Inflammation, suppurative		2 (4%)	
Mineralization		4 (8%)	
Alveolar epithelium, hyperplasia	5 (10%)	26 (52%)	38 (76%)
Alveolus, hemorrhage, focal	1 (2%)		
Alveolus, metaplasia, squamous			2 (4%)
Artery, thrombosis	1 (2%)		
Interstitium, fibrosis, focal	1 (2%)	16 (32%)	33 (66%)
Interstitium, mineralization	2 (4%)	1 (2%)	4 (8%)
Peribronchial, hyperplasia, histiocytic		12 (24%)	8 (16%)
Nose	(49)	(48)	(47)
Inflammation, suppurative	2 (4%)	1 (2%)	
Lumen, foreign body	1 (2%)		
Lumen, hemorrhage			1 (2%)
Mucosa, inflammation, suppurative	4 (8%)	5 (10%)	2 (4%)
Nasolacrimal duct, inflammation, suppurative		1 (2%)	
Respiratory epithelium, hyperplasia		3 (6%)	14 (30%)
Trachea	(49)	(50)	(48)
Inflammation, suppurative	3 (6%)		1 (2%)
Special Senses System			
Eye	(3)	(2)	(2)
Cataract	1 (33%)	1 (50%)	2 (100%)
Inflammation, chronic			1 (50%)
Cornea, inflammation, necrotizing			1 (50%)
Cornea, necrosis	1 (33%)		
Lens, cataract	1 (33%)		
Retina, degeneration	2 (67%)	1 (50%)	1 (50%)
Urinary System			
Kidney	(49)	(49)	(48)
Calculus micro observation only			1 (2%)
Cyst	3 (6%)		1 (2%)
Hydronephrosis		1 (2%)	1 (2%)
Nephropathy	45 (92%)	47 (96%)	43 (90%)
Medulla, inflammation		1 (2%)	1 (2%)
Renal tubule, necrosis		1 (2%)	
Ureter			(1)
Calculus micro observation only			1 (100%)
Urethra			(1)
Fibrosis			1 (100%)
Urinary bladder	(49)	(48)	(47)
Calculus gross observation			1 (2%)
Inflammation	1 (2%)		
Mucosa, hyperplasia			1 (2%)

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE LIFETIME INHALATION STUDY OF TALC

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the Lifetime Inhalation Study of Talc[a]

	0 mg/m^3	6 mg/m^3	18 mg/m^3
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Moribund	28	17	27
Natural deaths	11	19	14
Survivors			
Terminal sacrifice	11	13	9
Missing		1	
Animals examined microscopically	50	49	50
Alimentary System			
Intestine small, ileum	(44)	(32)	(38)
Liver	(50)	(48)	(50)
Granulosa-theca tumor malignant, metastatic, ovary			1 (2%)
Hepatocellular carcinoma		1 (2%)	
Neoplastic nodule		3 (6%)	1 (2%)
Pancreas	(50)	(46)	(49)
Pharynx			(1)
Squamous cell carcinoma			1 (100%)
Salivary glands	(50)	(48)	(50)
Fibrosarcoma			1 (2%)
Sarcoma		1 (2%)	
Stomach, forestomach	(50)	(45)	(49)
Stomach, glandular	(50)	(47)	(50)
Tongue		(2)	
Sarcoma, metastatic		1 (50%)	
Squamous cell papilloma		1 (50%)	
Tooth		(1)	
Adamantinoma benign		1 (100%)	
Cardiovascular System			
Heart	(50)	(48)	(50)
Granulosa-theca tumor malignant, metastatic, ovary			1 (2%)
Endocrine System			
Adrenal gland, cortex	(50)	(47)	(49)
Granulosa-theca tumor malignant, metastatic, ovary			1 (2%)
Adrenal gland, medulla	(48)	(47)	(49)
Granulosa-theca tumor malignant, metastatic, ovary			1 (2%)
Pheochromocytoma malignant		1 (2%)	7 (14%)
Pheochromocytoma benign	13 (27%)	10 (21%)	11 (22%)
Bilateral, pheochromocytoma malignant			3 (6%)
Bilateral, pheochromocytoma benign		4 (9%)	7 (14%)
Islets, pancreatic	(50)	(45)	(49)
Adenoma	1 (2%)	1 (2%)	1 (2%)
Parathyroid gland	(43)	(42)	(47)
Pituitary gland	(50)	(47)	(50)
Pars distalis, adenoma	19 (38%)	18 (38%)	21 (42%)
Pars distalis, carcinoma	3 (6%)	3 (6%)	2 (4%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the Lifetime Inhalation Study of Talc (continued)

	0 mg/m³	6 mg/m³	18 mg/m³
Endocrine System (continued)			
Thyroid gland	(50)	(47)	(49)
Bilateral, C-cell, carcinoma	1 (2%)		
C-cell, adenoma	5 (10%)		6 (12%)
C-cell, carcinoma	2 (4%)	2 (4%)	2 (4%)
Follicular cell, adenoma		1 (2%)	
General Body System			
None			
Genital System			
Clitoral gland	(47)	(44)	(46)
Adenoma			1 (2%)
Carcinoma	2 (4%)		1 (2%)
Ovary	(50)	(47)	(50)
Granulosa cell tumor malignant	1 (2%)		
Granulosa cell tumor benign		2 (4%)	
Granulosa-theca tumor benign		1 (2%)	
Bilateral, granulosa-theca tumor malignant			1 (2%)
Uterus	(50)	(48)	(50)
Polyp stromal	5 (10%)	7 (15%)	4 (8%)
Sarcoma stromal		1 (2%)	
Hematopoietic System			
Bone marrow	(50)	(43)	(49)
Lymph node	(50)	(48)	(50)
Lymph node, bronchial	(46)	(47)	(47)
Adenocarcinoma, metastatic, thyroid gland	1 (2%)		
Squamous cell carcinoma, metastatic, lung			1 (2%)
Lymph node, mandibular	(47)	(46)	(47)
Sarcoma, metastatic		1 (2%)	
Lymph node, mediastinal	(47)	(44)	(47)
Adenocarcinoma, metastatic, thyroid gland	1 (2%)		
Carcinoma, metastatic, uncertain primary site			1 (2%)
Fibrosarcoma, metastatic, skin			1 (2%)
Granulosa-theca tumor malignant, metastatic, ovary			1 (2%)
Lymph node, mesenteric	(49)	(47)	(47)
Spleen	(50)	(48)	(50)
Thymus	(47)	(44)	(47)
Mixed tumor malignant		1 (2%)	
Myxoma		1 (2%)	
Schwannoma benign			1 (2%)
Thymoma benign	1 (2%)		
Integumentary System			
Mammary gland	(50)	(48)	(50)
Adenocarcinoma	2 (4%)		2 (4%)
Adenoma	1 (2%)	2 (4%)	2 (4%)
Fibroadenoma	11 (22%)	10 (21%)	13 (26%)
Fibroma	1 (2%)	1 (2%)	
Fibrosarcoma			1 (2%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the Lifetime Inhalation Study of Talc (continued)

	0 mg/m³	6 mg/m³	18 mg/m³
Integumentary System (continued)			
Skin	(50)	(49)	(50)
Keratoacanthoma		1 (2%)	1 (2%)
Subcutaneous tissue, fibrosarcoma		1 (2%)	1 (2%)
Musculoskeletal System			
Bone	(50)	(48)	(50)
Mandible, sarcoma	1 (2%)		
Mandible, sarcoma, metastatic		1 (2%)	
Skeletal muscle	(1)	(1)	
Liposarcoma		1 (100%)	
Nervous System			
Brain	(50)	(48)	(50)
Astrocytoma benign	1 (2%)		
Carcinoma, metastatic, pituitary gland	2 (4%)	1 (2%)	1 (2%)
Ependymoma malignant	1 (2%)		
Respiratory System			
Larynx	(50)	(48)	(48)
Adenocarcinoma, metastatic, thyroid gland	1 (2%)		
Lung	(50)	(48)	(50)
Adenocarcinoma, metastatic, multiple, mammary gland	1 (2%)		
Alveolar/bronchiolar adenoma	1 (2%)		8 (16%)
Alveolar/bronchiolar adenoma, multiple			1 (2%)
Alveolar/bronchiolar carcinoma			4 (8%)
Alveolar/bronchiolar carcinoma, multiple			1 (2%)
Granulosa-theca tumor malignant, metastatic, ovary			1 (2%)
Squamous cell carcinoma			1 (2%)
Special Senses System			
None			
Urinary System			
Kidney	(49)	(47)	(49)
Lipoma		1 (2%)	
Urinary bladder	(50)	(45)	(50)
Systemic Lesions			
Multiple organs[b]	(50)	(49)	(50)
Leukemia mononuclear	13 (26%)	20 (41%)	18 (36%)
Lymphoma malignant lymphocytic		2 (4%)	
Lymphoma malignant mixed		1 (2%)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the Lifetime Inhalation Study of Talc (continued)

	0 mg/m³	6 mg/m³	18 mg/m³
Tumor Summary			
Total animals with primary neoplasms[c]	44	47	49
Total primary neoplasms	85	100	124
Total animals with benign neoplasms	38	35	39
Total benign neoplasms	59	65	78
Total animals with malignant neoplasms	23	31	35
Total malignant neoplasms	26	35	46
Total animals with metastatic neoplasms	4	3	4
Total metastatic neoplasms	6	8	10
Total animals with malignant neoplasms, uncertain primary site			1

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.
[b] Number of animals with any tissue examined microscopically
[c] Primary tumors: all tumors except metastatic tumors

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Lifetime Inhalation Study of Talc: 0 mg/m³

Number of Days on Study	370	390	398	558	568	584	586	599	626	634	647	677	678	688	696	716	719	727	731	762	766	767	768	772	779
Carcass ID Number	3351	4301	3771	3061	3501	3571	4321	4291	3581	3841	3021	3761	4021	3081	3591	3271	3051	4061	3971	3821	3511	3281	3261	3311	4081
Alimentary System																									
Esophagus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	+	+	+	+	+	+	+	A	+	+	+	A	A	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	M	+	+	+	A	+	M	M	M	+	+	+	+	+	+	M	+	+	M	+	+	+	+
Intestine small	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	A	A	A	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	+	+	A	+	+	A	+	+	+	+	A	+	+	+	A	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery												+													
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel																	+								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+
Pheochromocytoma benign													X					X				X	X		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X		X	X	X									X	X		X			X	X
Pars distalis, carcinoma															X										
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, carcinoma												X													
C-cell, adenoma																									
C-cell, carcinoma																									
General Body System																									
None																									

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Lifetime Inhalation Study of Talc: 0 mg/m³ (continued)

Number of Days on Study	7	7	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	
	8	8	0	0	0	1	1	1	2	2	3	4	4	5	6	6	6	6	6	6	6	6	6	6	6	
	6	9	0	5	8	3	6	7	4	7	5	1	6	9	2	2	2	2	2	3	3	3	3	3	3	
Carcass ID Number	4	3	3	3	3	4	3	4	3	3	3	3	4	4	3	3	3	3	3	3	3	3	4	4	4	**Total**
	2	1	5	3	0	2	7	2	8	5	7	5	0	2	0	1	2	3	3	8	8	9	0	0	2	**Tissues/**
	5	1	5	6	1	4	3	7	3	2	4	6	3	2	3	2	9	0	2	0	1	9	0	7	8	**Tumors**
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	38
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel		+				+																				3
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign			X		X			X		X						X	X		X				X	X		13
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X																	1
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X		X	X		X			X		X	X										X	X		X	19
Pars distalis, carcinoma										X					X											3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, carcinoma																										1
C-cell, adenoma				X								X		X	X									X		5
C-cell, carcinoma	X					X																				2
General Body System																										
None																										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Lifetime Inhalation Study of Talc: 0 mg/m³ (continued)

Number of Days on Study	3	3	3	5	5	5	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7
	7	9	9	5	6	8	8	9	2	3	4	7	7	8	9	1	1	2	3	6	6	6	6	7	7
	0	0	8	8	8	4	6	9	6	4	7	7	8	8	6	6	9	7	1	2	6	7	8	2	9
Carcass ID Number	3	4	3	3	3	3	4	4	3	3	3	3	4	3	3	3	3	4	3	3	3	3	3	3	4
	3	3	7	0	5	5	3	2	5	8	0	7	0	0	5	2	0	0	9	8	5	2	2	3	0
	5	0	7	6	0	7	2	9	8	4	2	6	2	8	9	7	5	6	7	2	1	8	6	1	8
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Genital System																									
Clitoral gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant																						X			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal			X																						
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, thyroid gland												X													
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Lymph node, mediastinal	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, thyroid gland												X													
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma benign																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma	X						X																		
Adenoma																									
Fibroadenoma										X			X								X				
Fibroma															X										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mandible, sarcoma																	X								
Skeletal muscle			+																						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma benign																					X				
Carcinoma, metastatic, pituitary gland															X										
Ependymoma malignant																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Lifetime Inhalation Study of Talc: 0 mg/m³ (continued)

Number of Days on Study	7	7	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	
	8	8	0	0	0	1	1	1	2	2	3	4	4	5	6	6	6	6	6	6	6	6	6	6	6	
	6	9	0	5	8	3	6	7	4	7	5	1	6	9	2	2	2	2	2	3	3	3	3	3	3	
	4	3	3	3	3	4	3	4	3	3	3	3	4	4	3	3	3	3	3	3	3	3	4	4	4	
Carcass ID Number	2	1	5	3	0	2	7	2	8	5	7	5	0	2	0	1	2	3	3	8	8	9	0	0	2	**Total**
	5	1	5	6	1	4	3	7	3	2	4	6	3	2	3	2	9	0	2	0	1	9	0	7	8	**Tissues/**
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	**Tumors**
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma																							X	X		2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor malignant																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal		X	X		X											X										5
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, bronchial	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	46
Adenocarcinoma, metastatic, thyroid gland																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	47
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	47
Adenocarcinoma, metastatic, thyroid gland																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymoma benign																									X	1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										2
Adenoma																				X						1
Fibroadenoma				X		X	X			X	X	X									X				X	11
Fibroma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mandible, sarcoma																										1
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma benign																										1
Carcinoma, metastatic, pituitary gland										X																2
Ependymoma malignant																			X							1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Lifetime Inhalation Study of Talc: 0 mg/m³ (continued)

Number of Days on Study	370	390	398	558	568	584	586	599	626	634	647	777	778	788	696	716	719	727	731	732	766	767	768	772	779
Carcass ID Number	3351	4301	3771	3061	3501	3571	4321	4291	3581	3841	3021	3761	4021	3081	3591	3271	3051	4061	3971	3821	3511	3281	3261	3311	4081
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, thyroid gland												X													
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, multiple, mammary gland							X																		
Alveolar/bronchiolar adenoma																									
Nose	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye				+																					
Harderian gland								+										+					+		
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X	X	X	X						X							X							X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Lifetime Inhalation Study of Talc: 0 mg/m³ (continued)

Number of Days on Study	7 8 6	7 8 9	8 0 0	8 0 5	8 0 8	8 1 3	8 1 6	8 1 7	8 2 4	8 2 7	8 3 5	8 4 1	8 4 6	8 5 9	8 6 2	8 6 2	8 6 2	8 6 2	8 6 2	8 6 3	8 6 3	8 6 3	8 6 3	8 6 3	8 6 3	
Carcass ID Number	4 2 5 1	3 1 1 1	3 5 5 1	3 3 6 1	3 0 1 1	4 2 4 1	3 7 3 1	4 2 7 1	3 8 3 1	3 5 2 1	3 7 4 1	3 5 6 1	4 0 3 1	4 2 2 1	3 0 3 1	3 1 2 1	3 2 9 1	3 3 0 1	3 3 2 1	3 8 0 1	3 8 1 1	3 9 9 1	4 0 0 1	4 0 7 1	4 2 8 1	**Total Tissues/ Tumors**
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, thyroid gland																										1
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, multiple, mammary gland																										1
Alveolar/bronchiolar adenoma				X																						1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																	+									2
Harderian gland									+	+																5
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X									X	X	X		X									X			13

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Lifetime Inhalation Study of Talc: 6 mg/m^3

Number of Days on Study	482	508	526	557	561	566	566	647	651	668	678	690	697	705	720	724	729	738	740	747	755	760	762	766	768
Carcass ID Number	0381	0481	0681	1371	0691	0431	0951	1101	0961	1411	1181	0451	0921	0701	0401	1091	1161	0891	1151	0391	1121	0671	0231	0171	0631
Alimentary System																									
Esophagus	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	A	+	+	+	+	+	A	+	+	+	+	+	+	A	+	A	+	+	+	+	A	+	A	+
Intestine large, cecum	+	A	+	+	+	+	+	A	A	+	+	+	A	+	A	+	A	+	+	A	A	A	+	A	A
Intestine large, colon	+	A	+	+	+	+	+	A	+	+	+	+	+	+	A	+	A	+	+	A	+	A	+	A	+
Intestine large, rectum	+	A	+	+	+	+	+	A	M	+	M	M	M	+	M	+	A	+	+	+	+	M	+	A	+
Intestine small	+	A	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	+	+	+	A	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	A	+	+	+	+	A	A	+	A	+	A	+	A	A	A	+	+	A	+	A	+	A	+
Intestine small, jejunum	+	A	+	+	+	+	+	A	A	+	+	+	+	+	A	+	A	+	+	A	+	A	+	A	+
Liver	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Neoplastic nodule																X									
Mesentery																							+		+
Pancreas	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic, metastatic																									
Sarcoma					X																				
Stomach	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Stomach, forestomach	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Stomach, glandular	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Tongue					+																				
Sarcoma, metastatic					X																				
Squamous cell papilloma																									
Tooth											+														
Adamantinoma benign											X														
Cardiovascular System																									
Blood vessel															+										
Heart	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign														X						X			X		
Bilateral, pheochromocytoma benign																						X			
Islets, pancreatic	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Adenoma																									
Parathyroid gland	+	A	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	I	+	+	+
Pituitary gland	+	A	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma													X	X				X	X	X	X				X
Pars distalis, carcinoma						X						X													
Thyroid gland	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
C-cell, carcinoma																									
Follicular cell, adenoma																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Lifetime Inhalation Study of Talc: 6 mg/m³ (continued)

Number of Days on Study	786	798	798	799	800	812	815	818	819	841	849	862	862	862	862	862	862	862	863	863	863	863	863	863	
Carcass ID Number	1441	0241	1431	1381	0851	0141	0371	0661	1171	0441	0641	0161	0181	0201	0211	0471	0621	0711	0861	0911	1111	1331	1361	1401	**Total Tissues/ Tumors**
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large, cecum	A	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	34
Intestine large, colon	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Intestine large, rectum	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	37
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, ileum	A	A	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	32
Intestine small, jejunum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular carcinoma																								X	1
Neoplastic nodule					X				X																3
Mesentery																									2
Pancreas	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant lymphocytic, metastatic		X																							1
Sarcoma																									1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	45
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Tongue				+																					2
Sarcoma, metastatic																									1
Squamous cell papilloma				X																					1
Tooth																									1
Adamantinoma benign																									1
Cardiovascular System																									
Blood vessel					+														+						3
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pheochromocytoma malignant											X														1
Pheochromocytoma benign						X			X		X	X				X			X	X					10
Bilateral, pheochromocytoma benign	X				X																			X	4
Islets, pancreatic	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma																								X	1
Parathyroid gland	+	M	M	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pars distalis, adenoma	X		X	X	X	X	X		X		X			X								X	X		18
Pars distalis, carcinoma													X												3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
C-cell, carcinoma								X		X															2
Follicular cell, adenoma					X																				1

Table B2
Individual Animal Tumor Pathology of Female Rats in the Lifetime Inhalation Study of Talc: 6 mg/m³ (continued)

Number of Days on Study	4	5	5	5	5	5	5	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7
	8	0	2	5	6	6	6	4	5	6	7	9	9	0	2	2	2	3	4	4	5	6	6	6	6
	2	8	6	7	1	6	6	7	1	8	8	0	7	5	0	4	9	8	0	7	5	0	2	6	8
Carcass ID Number	0	0	0	1	0	0	0	1	0	1	1	0	0	0	0	1	1	0	1	0	1	0	0	0	0
	3	4	6	3	6	4	9	1	9	4	1	4	9	7	4	0	1	8	1	3	1	6	2	1	6
	8	8	8	7	9	3	5	0	6	1	8	5	2	0	0	9	6	9	5	9	2	7	3	7	3
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
General Body System																									
None																									
Genital System																									
Clitoral gland	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	M
Ovary	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																									
Granulosa-theca tumor benign																		X							
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic, metastatic																									
Polyp stromal											X				X									X	
Sarcoma stromal				X																					
Hematopoietic System																									
Bone marrow	+	A	+	+	+	+	A	A	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+
Lymph node	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	+	A	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	A	+	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic					X																				
Lymph node, mediastinal	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Lymph node, mesenteric	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	A	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	I	+	+	+	+	+	+	+
Mixed tumor malignant									X																
Myxoma															X										
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Fibroadenoma	X				X																X	X		X	
Fibroma																									
Lymphoma malignant lymphocytic, metastatic																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Subcutaneous tissue, fibrosarcoma																			X						

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Lifetime Inhalation Study of Talc: 6 mg/m³ (continued)

Number of Days on Study	7	7	7	7	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	
	8	9	9	9	0	1	1	1	1	4	4	6	6	6	6	6	6	6	6	6	6	6	6	6	
	6	8	8	9	0	2	5	8	9	1	9	2	2	2	2	2	2	2	3	3	3	3	3	3	
Carcass ID Number	1	0	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	**Total**
	4	2	4	3	8	1	3	6	1	4	6	1	1	2	2	4	6	7	8	9	1	3	3	4	**Tissues/**
	4	4	3	8	5	4	7	6	7	4	4	6	8	0	1	7	2	1	6	1	1	3	6	0	**Tumors**
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	47
Granulosa cell tumor benign																				X	X				2
Granulosa-theca tumor benign																									1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	48
Lymphoma malignant lymphocytic, metastatic		X																							1
Polyp stromal									X				X			X		X							7
Sarcoma stromal																									1
Hematopoietic System																									
Bone marrow	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Sarcoma, metastatic																									1
Lymph node, mediastinal	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	44
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	44
Mixed tumor malignant																									1
Myxoma																									1
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																						X		X	2
Fibroadenoma			X								X			X	X								X		10
Fibroma													X												1
Lymphoma malignant lymphocytic, metastatic		X																							1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Keratoacanthoma																						X			1
Subcutaneous tissue, fibrosarcoma																									1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Lifetime Inhalation Study of Talc: 6 mg/m³ (continued)

Number of Days on Study	482	508	526	557	561	566	566	647	651	668	678	690	697	705	720	724	729	738	740	747	755	760	762	766	768
Carcass ID Number	0381	0481	0681	1371	0691	0431	0951	1101	0961	1411	1181	0451	0921	0701	0401	1091	1161	0891	1151	0391	1121	0671	0231	0171	0631
Musculoskeletal System																									
Bone	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mandible, sarcoma, metastatic					X																				
Skeletal muscle																									
Liposarcoma																									
Nervous System																									
Brain	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland						X																			
Respiratory System																									
Larynx	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+
Trachea	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland										+													+		
Urinary System																									
Kidney	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Lymphoma malignant lymphocytic, metastatic																									
Urinary bladder	+	A	+	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X				X	X		X		X	X				X	X		X		X		X	
Lymphoma malignant lymphocytic																X									
Lymphoma malignant mixed																				X					

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Lifetime Inhalation Study of Talc: 6 mg/m³ (continued)

Number of Days on Study	7	7	7	7	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	
	8	9	9	9	0	1	1	1	1	4	4	6	6	6	6	6	6	6	6	6	6	6	6	6	
	6	8	8	9	0	2	5	8	9	1	9	2	2	2	2	2	2	2	3	3	3	3	3	3	
Carcass ID Number	1	0	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	**Total**
	4	2	4	3	8	1	3	6	1	4	6	1	1	2	2	4	6	7	8	9	1	3	3	4	**Tissues/**
	4	4	3	8	5	4	7	6	7	4	4	6	8	0	1	7	2	1	6	1	1	3	6	0	**Tumors**
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mandible, sarcoma, metastatic																									1
Skeletal muscle																						+			1
Liposarcoma																						X			1
Nervous System																									
Brain	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, pituitary gland																									1
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Special Senses System																									
Harderian gland			+					+							+			+					+		7
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lipoma																						X			1
Lymphoma malignant lymphocytic, metastatic		X																							1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	45
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear			X											X	X	X				X	X	X	X	X	20
Lymphoma malignant lymphocytic		X																							2
Lymphoma malignant mixed																									1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Lifetime Inhalation Study of Talc: 18 mg/m³

Number of Days on Study	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7
	3	5	8	9	1	3	4	6	6	7	7	7	8	9	9	0	1	1	1	2	3	4	4	4	7
	6	8	6	4	5	3	6	0	1	5	6	8	4	3	7	6	0	6	7	4	9	0	6	7	3
Carcass ID Number	1	2	2	2	1	2	2	2	1	2	2	2	2	2	1	2	1	2	2	2	1	2	1	2	2
	6	8	1	1	8	8	3	8	8	8	0	5	0	4	8	0	6	8	3	5	8	6	9	3	0
	7	0	6	2	3	5	0	1	6	8	7	5	8	0	9	6	0	2	6	6	1	3	2	9	9
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	+	+	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Intestine large, colon	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Intestine large, rectum	+	M	A	M	+	A	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+
Intestine small	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Intestine small, ileum	+	+	A	+	+	A	A	+	+	+	+	+	A	+	A	+	+	+	A	+	A	+	A	+	+
Intestine small, jejunum	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor malignant, metastatic, ovary																X									
Neoplastic nodule																									
Pancreas	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx				+																					
Squamous cell carcinoma				X																					
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor malignant, metastatic, ovary																X									
Endocrine System																									
Adrenal gland	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor malignant, metastatic, ovary																X									
Adrenal gland, medulla	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor malignant, metastatic, ovary																X									
Pheochromocytoma malignant																									
Pheochromocytoma benign																							X		
Bilateral, pheochromocytoma malignant																									
Bilateral, pheochromocytoma benign															X		X								
Islets, pancreatic	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma							X																		
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Lifetime Inhalation Study of Talc: 18 mg/m³ (continued)

Number of Days on Study	7 8 4	7 8 6	7 9 6	8 0 3	8 2 2	8 2 3	8 2 8	8 2 9	8 3 5	8 4 1	8 4 1	8 4 2	8 4 8	8 5 0	8 5 4	8 5 7	8 6 2	8 6 2	8 6 2	8 6 2	8 6 2	8 6 3	8 6 3	8 6 3	8 6 3	
Carcass ID Number	2 5 7 1	2 8 7 1	2 3 3 1	2 5 3 1	1 6 2 1	1 6 4 1	1 5 7 1	2 7 7 1	2 1 5 1	1 9 0 1	1 9 1 1	2 0 5 1	2 5 8 1	2 6 4 1	2 3 1 1	1 6 5 1	1 5 8 1	1 6 3 1	1 6 6 1	1 8 2 1	2 3 2 1	2 3 8 1	2 5 4 1	2 5 9 1	2 8 6 1	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	A	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	43
Intestine large, colon	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	45
Intestine large, rectum	+	+	+	+	+	A	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	41
Intestine small	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	A	+	+	+	+	A	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	38
Intestine small, jejunum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa-theca tumor malignant, metastatic, ovary																										1
Neoplastic nodule																X										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pharynx																										1
Squamous cell carcinoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																X										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel										+																1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa-theca tumor malignant, metastatic, ovary																										1
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granulosa-theca tumor malignant, metastatic, ovary																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granulosa-theca tumor malignant, metastatic, ovary																										1
Pheochromocytoma malignant	X				X			X	X	X	X												X			7
Pheochromocytoma benign			X		X		X	X	X	X				X						X			X		X	11
Bilateral, pheochromocytoma malignant															X		X				X					3
Bilateral, pheochromocytoma benign						X							X						X			X		X		7
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	47

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Lifetime Inhalation Study of Talc: 18 mg/m³ (continued)

Number of Days on Study	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7
	3	5	8	9	1	3	4	6	6	7	7	7	8	9	9	0	1	1	1	2	3	4	4	4	7
	6	8	6	4	5	3	6	0	1	5	6	8	4	3	7	6	0	6	7	4	9	0	6	7	3
Carcass ID Number	1	2	2	2	1	2	2	2	1	2	2	2	2	2	1	2	1	2	2	2	1	2	1	2	2
	6	8	1	1	8	8	3	8	8	8	0	5	0	4	8	0	6	8	3	5	8	6	9	3	0
	7	0	6	2	3	5	0	1	6	8	7	5	8	0	9	6	0	2	6	6	1	3	2	9	9
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Endocrine System (continued)																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X		X		X		X		X							X				
Pars distalis, carcinoma											X									X					
Thyroid gland	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma												X	X												
C-cell, carcinoma										X	X														
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+
Adenoma																									
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, granulosa-theca tumor malignant																X									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal												X								X					
Hematopoietic System																									
Bone marrow	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+
Squamous cell carcinoma, metastatic, lung																X									
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uncertain primary site																									
Fibrosarcoma, metastatic, skin									X																
Granulosa-theca tumor malignant, metastatic, ovary																X									
Lymph node, mesenteric	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma benign																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Lifetime Inhalation Study of Talc: 18 mg/m^3 (continued)

Number of Days on Study	784	786	796	803	822	823	828	829	835	841	841	842	848	850	854	857	862	862	862	862	862	863	863	863	863	
Carcass ID Number	2571	2871	2331	2531	1621	1641	1571	2771	2151	1901	1911	2051	2581	2641	2311	1651	1581	1631	1661	1821	2321	2381	2541	2591	2861	**Total Tissues/ Tumors**
Endocrine System (continued)																										
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X		X	X			X	X	X	X	X	X	X	X		X				X	X		X	21
Pars distalis, carcinoma																										2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma							X	X											X					X		6
C-cell, carcinoma																										2
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	46
Adenoma									X																	1
Carcinoma																					X					1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, granulosa-theca tumor malignant																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal	X																								X	4
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell carcinoma, metastatic, lung																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	M	47
Carcinoma, metastatic, uncertain primary site				X																						1
Fibrosarcoma, metastatic, skin																										1
Granulosa-theca tumor malignant, metastatic, ovary																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Schwannoma benign																X										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Lifetime Inhalation Study of Talc: 18 mg/m³ (continued)

Number of Days on Study	536	558	586	594	613	633	646	660	661	675	676	678	684	693	697	706	710	716	717	724	739	740	746	747	773
Carcass ID Number	1671	2801	2161	2121	1831	2851	2301	2811	1861	2881	2071	2551	2081	2401	1891	2061	1601	2821	2361	2561	1811	2631	1921	2391	2091
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Adenoma																									
Fibroadenoma												X	X							X		X		X	
Fibrosarcoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma		X																							
Subcutaneous tissue, fibrosarcoma									X																
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland											X														
Respiratory System																									
Larynx	+	+	+	+	+	I	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																		X				X			
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma																									
Alveolar/bronchiolar carcinoma, multiple																									
Granulosa-theca tumor malignant, metastatic, ovary																X									
Squamous cell carcinoma																X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Harderian gland										+	+	+		+					+	+		+			+
Lacrimal gland																									
Urinary System																									
Kidney	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X		X	X		X		X			X				X				X			X	X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the Lifetime Inhalation Study of Talc: 18 mg/m³ (continued)

Number of Days on Study	7	7	7	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	
	8	8	9	0	2	2	2	2	3	4	4	4	5	5	5	6	6	6	6	6	6	6	6	6	6	
	4	6	6	3	2	3	8	9	5	1	1	2	8	0	4	7	2	2	2	2	2	3	3	3	3	
Carcass ID Number	2	2	2	2	1	1	1	2	2	1	1	2	2	2	2	1	1	1	1	1	2	2	2	2	2	**Total**
	5	8	3	5	6	6	5	7	1	9	9	0	5	6	3	6	5	6	6	8	3	3	5	5	8	**Tissues/**
	7	7	3	3	2	4	7	7	5	0	1	5	8	4	1	5	8	3	6	2	2	8	4	9	6	**Tumors**
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma					X						X															2
Adenoma								X					X													2
Fibroadenoma							X		X		X				X				X	X	X		X			13
Fibrosarcoma						X																				1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																										1
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X				X	X		X			X							X							8
Alveolar/bronchiolar adenoma, multiple								X																		1
Alveolar/bronchiolar carcinoma							X						X							X	X					4
Alveolar/bronchiolar carcinoma, multiple																								X		1
Granulosa-theca tumor malignant, metastatic, ovary																										1
Squamous cell carcinoma																										1
Nose	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye											+											+				2
Harderian gland	+			+								+	+	+		+									+	15
Lacrimal gland													+													1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X		X				X			X						X						X		X	18

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the Lifetime Inhalation Study of Talc

	0 mg/m³	6 mg/m³	18 mg/m³
Adrenal Medulla: Benign Pheochromocytoma			
Overall rates[a]	13/48 (27%)	14/47 (30%)	18/49 (37%)
Adjusted rates[b]	61.3%	59.7%	82.5%
Terminal rates[c]	5/11 (45%)	5/13 (38%)	6/9 (67%)
First incidence (days)	678	705	697
Life table tests[d]	P=0.135	P=0.529	P=0.183
Logistic regression tests[d]	P=0.185	P=0.541	P=0.225
Cochran-Armitage test[d]	P=0.180		
Fisher exact test[d]		P=0.474	P=0.212
Adrenal Medulla: Malignant Pheochromocytoma			
Overall rates	0/48 (0%)	1/47 (2%)	10/49 (20%)
Adjusted rates	0.0%	7.1%	56.9%
Terminal rates	0/11 (0%)	0/13 (0%)	3/9 (33%)
First incidence (days)	–[e]	849	784
Life table tests	P<0.001	P=0.531	P=0.002
Logistic regression tests	P<0.001	P=0.509	P=0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.495	P<0.001
Adrenal Medulla: Benign or Malignant Pheochromocytoma			
Overall rates	13/48 (27%)	14/47 (30%)	23/49 (47%)
Adjusted rates	61.3%	59.7%	95.2%
Terminal rates	5/11 (45%)	5/13 (38%)	8/9 (89%)
First incidence (days)	678	705	697
Life table tests	P=0.016	P=0.529	P=0.033
Logistic regression tests	P=0.014	P=0.541	P=0.024
Cochran-Armitage test	P=0.021		
Fisher exact test		P=0.474	P=0.034
Liver: Neoplastic Nodule			
Overall rates	0/50 (0%)	3/48 (6%)	1/50 (2%)
Adjusted rates	0.0%	13.6%	10.0%
Terminal rates	0/11 (0%)	0/13 (0%)	0/9 (0%)
First incidence (days)	–	724	857
Life table tests	P=0.550	P=0.114	P=0.464
Logistic regression tests	P=0.561	P=0.117	P=0.496
Cochran-Armitage test	P=0.556		
Fisher exact test		P=0.114	P=0.500
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Overall rates	0/50 (0%)	4/48 (8%)	1/50 (2%)
Adjusted rates	0.0%	20.2%	10.0%
Terminal rates	0/11 (0%)	1/13 (8%)	0/9 (0%)
First incidence (days)	–	724	857
Life table tests	P=0.575	P=0.066	P=0.464
Logistic regression tests	P=0.602	P=0.060	P=0.496
Cochran-Armitage test	P=0.599		
Fisher exact test		P=0.054	P=0.500

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the Lifetime Inhalation Study of Talc (continued)

	0 mg/m³	6 mg/m³	18 mg/m³
Lung: Alveolar/bronchiolar Adenoma			
Overall rates	1/50 (2%)	0/48 (0%)	9/50 (18%)
Adjusted rates	4.5%	0.0%	40.8%
Terminal rates	0/11 (0%)	0/13 (0%)	1/9 (11%)
First incidence (days)	805	–	716
Life table tests	P<0.001	P=0.529N	P=0.015
Logistic regression tests	P<0.001	P=0.503N	P=0.010
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.510N	P=0.008
Lung: Alveolar/bronchiolar Carcinoma			
Overall rates	0/50 (0%)	0/48 (0%)	5/50 (10%)
Adjusted rates	0.0%	0.0%	41.7%
Terminal rates	0/11 (0%)	0/13 (0%)	3/9 (33%)
First incidence (days)	–	–	828
Life table tests	P=0.002	–f	P=0.027
Logistic regression tests	P=0.003	–	P=0.028
Cochran-Armitage test	P=0.004		
Fisher exact test		–	P=0.028
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rates	1/50 (2%)	0/48 (0%)	13/50 (26%)
Adjusted rates	4.5%	0.0%	65.8%
Terminal rates	0/11 (0%)	0/13 (0%)	4/9 (44%)
First incidence (days)	805	–	716
Life table tests	P<0.001	P=0.529N	P=0.001
Logistic regression tests	P<0.001	P=0.503N	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.510N	P<0.001
Mammary Gland: Fibroadenoma			
Overall rates	11/50 (22%)	10/49 (20%)	13/50 (26%)
Adjusted rates	47.6%	41.4%	64.0%
Terminal rates	2/11 (18%)	3/13 (23%)	4/9 (44%)
First incidence (days)	634	482	678
Life table tests	P=0.304	P=0.489N	P=0.394
Logistic regression tests	P=0.363	P=0.508N	P=0.428
Cochran-Armitage test	P=0.343		
Fisher exact test		P=0.521N	P=0.408
Mammary Gland: Fibroma, Fibroadenoma, or Adenoma			
Overall rates	13/50 (26%)	13/49 (27%)	15/50 (30%)
Adjusted rates	54.7%	59.0%	68.6%
Terminal rates	3/11 (27%)	6/13 (46%)	4/9 (44%)
First incidence (days)	634	482	678
Life table tests	P=0.314	P=0.544N	P=0.404
Logistic regression tests	P=0.394	P=0.585	P=0.434
Cochran-Armitage test	P=0.371		
Fisher exact test		P=0.567	P=0.412

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the Lifetime Inhalation Study of Talc (continued)

	0 mg/m³	6 mg/m³	18 mg/m³
Mammary Gland: Fibroma, Fibroadenoma, Adenoma, or Adenocarcinoma			
Overall rates	15/50 (30%)	13/49 (27%)	16/50 (32%)
Adjusted rates	56.6%	59.0%	70.1%
Terminal rates	3/11 (27%)	6/13 (46%)	4/9 (44%)
First incidence (days)	370	482	678
Life table tests	P=0.378	P=0.386N	P=0.494
Logistic regression tests	P=0.457	P=0.425N	P=0.531
Cochran-Armitage test	P=0.430		
Fisher exact test		P=0.437N	P=0.500
Pituitary Gland (Pars Distalis): Adenoma			
Overall rates	19/50 (38%)	18/47 (38%)	21/50 (42%)
Adjusted rates	62.1%	60.5%	78.3%
Terminal rates	3/11 (27%)	3/13 (23%)	4/9 (44%)
First incidence (days)	568	697	633
Life table tests	P=0.360	P=0.512N	P=0.425
Logistic regression tests	P=0.409	P=0.557N	P=0.457
Cochran-Armitage test	P=0.380		
Fisher exact test		P=0.571	P=0.419
Pituitary Gland (Pars Distalis): Carcinoma			
Overall rates	3/50 (6%)	3/47 (6%)	2/50 (4%)
Adjusted rates	17.1%	12.2%	5.6%
Terminal rates	1/11 (9%)	1/13 (8%)	0/9 (0%)
First incidence (days)	696	566	676
Life table tests	P=0.438N	P=0.636N	P=0.506N
Logistic regression tests	P=0.427N	P=0.634	P=0.497N
Cochran-Armitage test	P=0.418N		
Fisher exact test		P=0.631	P=0.500N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma			
Overall rates	22/50 (44%)	21/47 (45%)	23/50 (46%)
Adjusted rates	69.8%	66.2%	79.5%
Terminal rates	4/11 (36%)	4/13 (31%)	4/9 (44%)
First incidence (days)	568	566	633
Life table tests	P=0.429	P=0.502N	P=0.488
Logistic regression tests	P=0.506	P=0.570N	P=0.545
Cochran-Armitage test	P=0.471		
Fisher exact test		P=0.554	P=0.500
Thyroid Gland (C-cell): Adenoma			
Overall rates	5/50 (10%)	0/47 (0%)	6/49 (12%)
Adjusted rates	33.5%	0.0%	34.0%
Terminal rates	2/11 (18%)	0/13 (0%)	2/9 (22%)
First incidence (days)	805	-	678
Life table tests	P=0.253	P=0.030N	P=0.467
Logistic regression tests	P=0.283	P=0.029N	P=0.505
Cochran-Armitage test	P=0.276		
Fisher exact test		P=0.033N	P=0.486

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the Lifetime Inhalation Study of Talc (continued)

	0 mg/m³	6 mg/m³	18 mg/m³
Thyroid Gland (C-cell): Carcinoma			
Overall rates	3/50 (6%)	2/47 (4%)	2/49 (4%)
Adjusted rates	11.1%	12.2%	4.9%
Terminal rates	0/11 (0%)	0/13 (0%)	0/9 (0%)
First incidence (days)	677	818	675
Life table tests	P=0.430N	P=0.507N	P=0.493N
Logistic regression tests	P=0.462N	P=0.516N	P=0.533N
Cochran-Armitage test	P=0.463N		
Fisher exact test		P=0.530N	P=0.510N
Thyroid Gland (C-cell): Adenoma or Carcinoma			
Overall rates	8/50 (16%)	2/47 (4%)	8/49 (16%)
Adjusted rates	40.9%	12.2%	37.2%
Terminal rates	2/11 (18%)	0/13 (0%)	2/9 (22%)
First incidence (days)	677	818	675
Life table tests	P=0.418	P=0.051N	P=0.579
Logistic regression tests	P=0.435	P=0.048N	P=0.599N
Cochran-Armitage test	P=0.414		
Fisher exact test		P=0.056N	P=0.590
Uterus: Stromal Polyp			
Overall rates	5/50 (10%)	7/49 (14%)	4/50 (8%)
Adjusted rates	22.3%	34.4%	19.5%
Terminal rates	1/11 (9%)	3/13 (23%)	1/9 (11%)
First incidence (days)	398	678	678
Life table tests	P=0.439N	P=0.400	P=0.532N
Logistic regression tests	P=0.376N	P=0.372	P=0.505N
Cochran-Armitage test	P=0.386N		
Fisher exact test		P=0.365	P=0.500N
Uterus: Stromal Polyp or Stromal Sarcoma			
Overall rates	5/50 (10%)	8/49 (16%)	4/50 (8%)
Adjusted rates	22.3%	35.8%	19.5%
Terminal rates	1/11 (9%)	3/13 (23%)	1/9 (11%)
First incidence (days)	398	557	678
Life table tests	P=0.412N	P=0.298	P=0.532N
Logistic regression tests	P=0.360N	P=0.265	P=0.505N
Cochran-Armitage test	P=0.363N		
Fisher exact test		P=0.264	P=0.500N
All Organs: Mononuclear Cell Leukemia			
Overall rates	13/50 (26%)	20/49 (41%)	18/50 (36%)
Adjusted rates	45.7%	73.3%	60.1%
Terminal rates	1/11 (9%)	8/13 (62%)	3/9 (33%)
First incidence (days)	390	526	536
Life table tests	P=0.234	P=0.164	P=0.232
Logistic regression tests	P=0.226	P=0.084	P=0.152
Cochran-Armitage test	P=0.250		
Fisher exact test		P=0.088	P=0.194

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the Lifetime Inhalation Study of Talc (continued)

	0 mg/m³	6 mg/m³	18 mg/m³
All Organs: Malignant Lymphoma			
Overall rates	0/50 (0%)	3/49 (6%)	0/50 (0%)
Adjusted rates	0.0%	10.3%	0.0%
Terminal rates	0/11 (0%)	0/13 (0%)	0/9 (0%)
First incidence (days)	-	724	-
Life table tests	P=0.525N	P=0.124	-
Logistic regression tests	P=0.497N	P=0.118	-
Cochran-Armitage test	P=0.499N		
Fisher exact test		P=0.117	-
All Organs: Benign Tumors			
Overall rates	38/50 (76%)	35/49 (71%)	39/50 (78%)
Adjusted rates	97.2%	96.9%	97.4%
Terminal rates	10/11 (91%)	12/13 (92%)	8/9 (89%)
First incidence (days)	398	482	558
Life table tests	P=0.338	P=0.350N	P=0.440
Logistic regression tests	P=0.544	P=0.312N	P=0.562N
Cochran-Armitage test	P=0.415		
Fisher exact test		P=0.387N	P=0.500
All Organs: Malignant Tumors			
Overall rates	23/50 (46%)	31/49 (63%)	35/50 (70%)
Adjusted rates	69.3%	85.8%	90.5%
Terminal rates	4/11 (36%)	9/13 (69%)	6/9 (67%)
First incidence (days)	370	526	536
Life table tests	P=0.054	P=0.189	P=0.061
Logistic regression tests	P=0.013	P=0.056	P=0.010
Cochran-Armitage test	P=0.016		
Fisher exact test		P=0.064	P=0.013
All Organs: Benign or Malignant Tumors			
Overall rates	44/50 (88%)	47/49 (96%)	49/50 (98%)
Adjusted rates	97.6%	97.9%	100.0%
Terminal rates	10/11 (91%)	12/13 (92%)	9/9 (100%)
First incidence (days)	370	482	536
Life table tests	P=0.248	P=0.447	P=0.279
Logistic regression tests	P=0.053	P=0.145	P=0.060
Cochran-Armitage test	P=0.049		
Fisher exact test		P=0.141	P=0.056

[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no tumors in animal group
[f] Value of statistic cannot be computed.

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Lifetime Inhalation Study of Talc[a]

	0 mg/m^3	6 mg/m^3	18 mg/m^3
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Moribund	28	17	27
Natural deaths	11	19	14
Survivors			
Terminal sacrifice	11	13	9
Missing		1	
Animals examined microscopically	50	49	50
Alimentary System			
Intestine large, cecum	(46)	(34)	(43)
Hemorrhage, focal		1 (3%)	
Inflammation	11 (24%)	1 (3%)	6 (14%)
Parasite metazoan	7 (15%)	3 (9%)	6 (14%)
Ulcer	1 (2%)	1 (3%)	1 (2%)
Intestine large, colon	(48)	(41)	(45)
Inflammation		1 (2%)	2 (4%)
Parasite metazoan	2 (4%)	3 (7%)	3 (7%)
Intestine large, rectum	(38)	(37)	(41)
Inflammation	4 (11%)		
Parasite metazoan	2 (5%)	1 (3%)	1 (2%)
Intestine small, duodenum	(48)	(44)	(47)
Necrosis, focal	1 (2%)		
Intestine small, ileum	(44)	(32)	(38)
Hyperplasia, lymphoid	2 (5%)		
Liver	(50)	(48)	(50)
Atrophy		1 (2%)	1 (2%)
Basophilic focus	27 (54%)	17 (35%)	21 (42%)
Clear cell focus	1 (2%)	2 (4%)	1 (2%)
Cyst multilocular	1 (2%)		
Degeneration, cystic		2 (4%)	1 (2%)
Eosinophilic focus	2 (4%)	5 (10%)	4 (8%)
Fatty change	18 (36%)	18 (38%)	14 (28%)
Hematopoietic cell proliferation	1 (2%)		
Infiltration cellular, mononuclear cell			1 (2%)
Inflammation, granulomatous, focal	13 (26%)	3 (6%)	4 (8%)
Inflammation, necrotizing, focal		1 (2%)	
Inflammation, suppurative	1 (2%)		
Necrosis, focal	5 (10%)	1 (2%)	2 (4%)
Pigmentation, hemosiderin	1 (2%)		
Thrombosis			1 (2%)
Bile duct, hyperplasia	36 (72%)	38 (79%)	36 (72%)
Centrilobular, atrophy		2 (4%)	6 (12%)
Centrilobular, degeneration	10 (20%)	14 (29%)	10 (20%)
Centrilobular, necrosis	2 (4%)	2 (4%)	2 (4%)
Hepatocyte, atrophy, focal			1 (2%)
Serosa, thrombosis		3 (6%)	
Mesentery	(1)	(2)	
Granuloma	1 (100%)	1 (50%)	
Inflammation, chronic active		1 (50%)	

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Lifetime Inhalation Study of Talc (continued)

	0 mg/m^3	6 mg/m^3	18 mg/m^3
Alimentary System (continued)			
Pancreas	(50)	(46)	(49)
Hyperplasia, nodular	1 (2%)		
Inflammation		1 (2%)	
Lobules, atrophy	7 (14%)	7 (15%)	9 (18%)
Salivary glands	(50)	(48)	(50)
Inflammation	2 (4%)		
Stomach, forestomach	(50)	(45)	(49)
Hyperkeratosis	1 (2%)		1 (2%)
Inflammation	1 (2%)		2 (4%)
Mineralization		1 (2%)	
Ulcer	9 (18%)	4 (9%)	3 (6%)
Stomach, glandular	(50)	(47)	(50)
Erosion			1 (2%)
Inflammation	1 (2%)	1 (2%)	
Mineralization	2 (4%)	2 (4%)	2 (4%)
Ulcer	3 (6%)	2 (4%)	3 (6%)
Ulcer, multiple	1 (2%)		1 (2%)
Arteriole, muscularis, lamina propria, mineralization		1 (2%)	
Cardiovascular System			
Blood vessel	(3)	(3)	(1)
Aorta, mineralization		3 (100%)	1 (100%)
Mesenteric artery, aneurysm	1 (33%)		
Mesenteric artery, inflammation	3 (100%)		
Mesenteric artery, mineralization		1 (33%)	1 (100%)
Mesenteric artery, thrombosis	1 (33%)	1 (33%)	
Heart	(50)	(48)	(50)
Cardiomyopathy	35 (70%)	40 (83%)	36 (72%)
Inflammation, focal	1 (2%)		1 (2%)
Atrium, thrombosis	5 (10%)	8 (17%)	5 (10%)
Myocardium, embolus		2 (4%)	
Myocardium, inflammation, focal		1 (2%)	
Myocardium, mineralization	1 (2%)	4 (8%)	3 (6%)
Endocrine System			
Adrenal gland, cortex	(50)	(47)	(49)
Degeneration, cystic	1 (2%)		
Degeneration, fatty	3 (6%)		
Degeneration, focal	1 (2%)	1 (2%)	
Hyperplasia, diffuse		1 (2%)	1 (2%)
Hyperplasia, focal	9 (18%)	12 (26%)	13 (27%)
Necrosis			2 (4%)
Necrosis, focal	1 (2%)	1 (2%)	
Pigmentation, hemosiderin	1 (2%)		
Adrenal gland, medulla	(48)	(47)	(49)
Cyst	1 (2%)		
Hyperplasia	20 (42%)	18 (38%)	14 (29%)
Bilateral, hyperplasia	2 (4%)	2 (4%)	2 (4%)
Parathyroid gland	(43)	(42)	(47)
Hyperplasia	3 (7%)	4 (10%)	2 (4%)
Bilateral, hyperplasia	1 (2%)		

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Lifetime Inhalation Study of Talc
(continued)

	0 mg/m³	6 mg/m³	18 mg/m³
Endocrine System (continued)			
Pituitary gland	(50)	(47)	(50)
Cyst	2 (4%)		1 (2%)
Pars distalis, hyperplasia	10 (20%)	6 (13%)	4 (8%)
Pars distalis, necrosis			1 (2%)
Thyroid gland	(50)	(47)	(49)
C-cell, hyperplasia	10 (20%)	8 (17%)	4 (8%)
General Body System			
None			
Genital System			
Clitoral gland	(47)	(44)	(46)
Hyperplasia	2 (4%)		1 (2%)
Inflammation	1 (2%)	1 (2%)	1 (2%)
Ovary	(50)	(47)	(50)
Cyst	5 (10%)		1 (2%)
Uterus	(50)	(48)	(50)
Cyst	1 (2%)	1 (2%)	1 (2%)
Inflammation	1 (2%)	1 (2%)	
Endometrium, hyperplasia	3 (6%)		
Lamina propria, fibrosis	20 (40%)	39 (81%)	19 (38%)
Hematopoietic System			
Bone marrow	(50)	(43)	(49)
Atrophy	1 (2%)	2 (5%)	1 (2%)
Hyperplasia, histiocytic	1 (2%)		1 (2%)
Inflammation, granulomatous, focal	1 (2%)		
Myelofibrosis	1 (2%)	3 (7%)	3 (6%)
Necrosis, focal		1 (2%)	
Myeloid cell, hyperplasia	2 (4%)	2 (5%)	3 (6%)
Lymph node	(50)	(48)	(50)
Axillary, hemorrhage, chronic			1 (2%)
Lymph node, bronchial	(46)	(47)	(47)
Cyst	1 (2%)		
Fibrosis		1 (2%)	
Hemorrhage, chronic		1 (2%)	
Hyperplasia, histiocytic		40 (85%)	45 (96%)
Inflammation, suppurative	1 (2%)		
Pigmentation, hemosiderin	1 (2%)		
Lymph node, mandibular	(47)	(46)	(47)
Hyperplasia, lymphoid		1 (2%)	1 (2%)
Hyperplasia, plasma cell	2 (4%)	1 (2%)	1 (2%)
Inflammation, chronic active	1 (2%)		1 (2%)
Inflammation, suppurative			1 (2%)
Lymph node, mediastinal	(47)	(44)	(47)
Hemorrhage, chronic	1 (2%)		
Hyperplasia, histiocytic		33 (75%)	40 (85%)
Hyperplasia, lymphoid	1 (2%)		1 (2%)
Inflammation, chronic active			1 (2%)
Inflammation, suppurative	1 (2%)	1 (2%)	

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Lifetime Inhalation Study of Talc (continued)

	0 mg/m^3	6 mg/m^3	18 mg/m^3
Hematopoietic System (continued)			
Lymph node, mesenteric	(49)	(47)	(47)
Hemorrhage		1 (2%)	
Hyperplasia, lymphoid	2 (4%)	1 (2%)	2 (4%)
Hyperplasia, plasma cell	1 (2%)		
Inflammation, chronic active	4 (8%)	1 (2%)	
Inflammation, granulomatous			1 (2%)
Spleen	(50)	(48)	(50)
Atrophy	2 (4%)	2 (4%)	2 (4%)
Fibrosis, focal	3 (6%)	1 (2%)	1 (2%)
Hematopoietic cell proliferation	4 (8%)	6 (13%)	7 (14%)
Hyperplasia, lymphoid			1 (2%)
Inflammation, granulomatous, focal	1 (2%)		
Pigmentation, hemosiderin	2 (4%)		
Capsule, hemorrhage			1 (2%)
Thymus	(47)	(44)	(47)
Inflammation	1 (2%)		
Integumentary System			
Mammary gland	(50)	(48)	(50)
Galactocele		1 (2%)	
Hyperplasia, cystic		2 (4%)	
Lobules, hyperplasia			1 (2%)
Skin	(50)	(49)	(50)
Inflammation, focal	1 (2%)		
Musculoskeletal System			
Bone	(50)	(48)	(50)
Fibrous osteodystrophy	4 (8%)	3 (6%)	4 (8%)
Hyperostosis	4 (8%)	1 (2%)	3 (6%)
Pelvis, fracture	1 (2%)		
Vertebra, cyst	1 (2%)		
Nervous System			
Brain	(50)	(48)	(50)
Compression	8 (16%)	7 (15%)	9 (18%)
Hemorrhage		1 (2%)	1 (2%)
Hydrocephalus			1 (2%)
Inflammation, focal		1 (2%)	
White matter, necrosis, focal			2 (4%)
Respiratory System			
Larynx	(50)	(48)	(48)
Inflammation, necrotizing			1 (2%)
Inflammation, suppurative	2 (4%)	1 (2%)	1 (2%)
Lung	(50)	(48)	(50)
Crystals, focal	1 (2%)		
Cyst		1 (2%)	5 (10%)
Cyst, multiple			2 (4%)
Edema	1 (2%)		
Hemorrhage		1 (2%)	1 (2%)
Hyperplasia, adenomatous, diffuse			2 (4%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Lifetime Inhalation Study of Talc
(continued)

	0 mg/m³	6 mg/m³	18 mg/m³
Respiratory System (continued)			
Lung (continued)			
Inflammation, granulomatous	2 (4%)	47 (98%)	50 (100%)
Inflammation, suppurative	2 (4%)	1 (2%)	
Mineralization		2 (4%)	
Alveolar epithelium, hyperplasia	2 (4%)	27 (56%)	47 (94%)
Alveolus, metaplasia, squamous			8 (16%)
Bronchus, epithelium, degeneration, focal	1 (2%)		
Interstitium, fibrosis			1 (2%)
Interstitium, fibrosis, focal	1 (2%)	24 (50%)	44 (88%)
Interstitium, mineralization		1 (2%)	1 (2%)
Peribronchial, hyperplasia, histiocytic		8 (17%)	9 (18%)
Nose	(48)	(45)	(48)
Inflammation, suppurative		1 (2%)	
Lumen, foreign body			1 (2%)
Mucosa, inflammation, suppurative		3 (7%)	5 (10%)
Nasolacrimal duct, inflammation, suppurative	1 (2%)		
Nerve, developmental malformation	1 (2%)		
Olfactory epithelium, metaplasia		1 (2%)	
Respiratory epithelium, hyperplasia	1 (2%)	1 (2%)	2 (4%)
Respiratory epithelium, metaplasia, squamous		1 (2%)	
Trachea	(50)	(48)	(50)
Inflammation, necrotizing			1 (2%)
Inflammation, suppurative	3 (6%)	1 (2%)	2 (4%)
Special Senses System			
Eye	(2)		(2)
Cataract	2 (100%)		2 (100%)
Retina, degeneration	2 (100%)		2 (100%)
Harderian gland	(5)	(7)	(15)
Inflammation	4 (80%)	3 (43%)	3 (20%)
Urinary System			
Kidney	(49)	(47)	(49)
Abscess	1 (2%)		
Cyst		1 (2%)	1 (2%)
Cyst, multiple	1 (2%)		
Embolus, multiple		1 (2%)	
Infarct	1 (2%)		
Infarct, multiple			1 (2%)
Inflammation	1 (2%)	1 (2%)	
Nephropathy	44 (90%)	43 (91%)	42 (86%)
Capsule, inflammation		1 (2%)	
Medulla, inflammation		1 (2%)	1 (2%)
Renal tubule, necrosis	1 (2%)		2 (4%)
Urinary bladder	(50)	(45)	(50)
Inflammation			1 (2%)

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR INHALATION STUDY OF TALC

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Talc[a]

	0 mg/m^3	6 mg/m^3	18 mg/m^3
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Moribund	1	2	3
Natural deaths	16	18	14
Survivors			
Terminal sacrifice	30	28	32
Missexed	1	1	0
Missing	2	1	1
Animals examined microscopically	46	47	49
Alimentary System			
Gallbladder	(31)	(29)	(35)
Intestine large, colon	(36)	(38)	(39)
Intestine small, duodenum	(32)	(30)	(34)
Intestine small, ileum	(33)	(32)	(35)
Adenocarcinoma		1 (3%)	
Liver	(45)	(47)	(48)
Hemangiosarcoma	1 (2%)		1 (2%)
Hemangiosarcoma, metastatic, spleen	1 (2%)		
Hepatocellular carcinoma	6 (13%)	5 (11%)	11 (23%)
Hepatocellular adenoma	1 (2%)	8 (17%)	4 (8%)
Hepatocellular adenoma, multiple	2 (4%)	1 (2%)	
Pancreas	(42)	(39)	(42)
Hepatocellular carcinoma, metastatic, liver	1 (2%)		
Salivary glands	(45)	(46)	(47)
Stomach, glandular	(39)	(43)	(43)
Cardiovascular System			
Heart	(45)	(46)	(49)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Endocrine System			
Adrenal gland	(43)	(46)	(47)
Spindle cell, adenoma	1 (2%)	1 (2%)	1 (2%)
Adrenal gland, cortex	(43)	(46)	(47)
Adenoma		1 (2%)	1 (2%)
Adrenal gland, medulla	(39)	(39)	(42)
Pheochromocytoma malignant	1 (3%)		
Pituitary gland	(44)	(44)	(46)
Adenoma	1 (2%)		
Pars intermedia, adenoma		2 (5%)	
Thyroid gland	(45)	(46)	(45)
Follicular cell, adenoma			2 (4%)
General Body System			
Tissue NOS		(3)	(2)
Hemangioma			1 (50%)
Hemangiosarcoma, metastatic, spleen			1 (50%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Talc (continued)

	0 mg/m³	6 mg/m³	18 mg/m³
Genital System			
Epididymis	(39)	(39)	(42)
Prostate	(40)	(43)	(44)
Seminal vesicle	(41)	(43)	(39)
Testes	(43)	(44)	(45)
Hemangiosarcoma	1 (2%)		
Hematopoietic System			
Bone marrow	(40)	(42)	(43)
Hemangiosarcoma, metastatic, spleen	1 (3%)		
Lymph node	(45)	(46)	(48)
Lymph node, bronchial	(32)	(39)	(44)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Lymph node, mandibular	(23)	(23)	(19)
Hemangiosarcoma, metastatic, spleen			1 (5%)
Lymph node, mediastinal	(9)	(10)	(7)
Lymph node, mesenteric	(36)	(39)	(40)
Hemangiosarcoma, metastatic, spleen			1 (3%)
Spleen	(44)	(44)	(47)
Hemangiosarcoma	2 (5%)		2 (4%)
Thymus	(34)	(33)	(40)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (3%)
Integumentary System			
None			
Musculoskeletal System			
Bone	(46)	(47)	(49)
Hemangiosarcoma, metastatic, spleen			1 (2%)
Skeletal muscle			(1)
Thoracic, alveolar/bronchiolar carcinoma, metastatic, lung			1 (100%)
Nervous System			
None			
Respiratory System			
Lung	(45)	(47)	(48)
Alveolar/bronchiolar adenoma	6 (13%)	4 (9%)	7 (15%)
Alveolar/bronchiolar adenoma, multiple			2 (4%)
Alveolar/bronchiolar carcinoma	6 (13%)	2 (4%)	2 (4%)
Alveolar/bronchiolar carcinoma, multiple	1 (2%)		
Hemangiosarcoma, metastatic, liver	1 (2%)		
Hemangiosarcoma, metastatic, spleen			1 (2%)
Hepatocellular carcinoma, metastatic, liver		1 (2%)	2 (4%)
Special Senses System			
Harderian gland	(1)		(4)
Adenoma	1 (100%)		4 (100%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Talc (continued)

	0 mg/m³	6 mg/m³	18 mg/m³
Urinary System			
Kidney	(45)	(46)	(48)
Carcinoma, metastatic, uncertain primary site	1 (2%)		
Urinary bladder	(43)	(38)	(43)
Sarcoma	1 (2%)		
Systemic Lesions			
Multiple organs[b]	(46)	(47)	(49)
Lymphoma malignant lymphocytic		1 (2%)	
Lymphoma malignant mixed	2 (4%)		
Lymphoma malignant undifferentiated cell	3 (7%)		
Tumor Summary			
Total animals with primary neoplasms[c]	26	20	28
Total primary neoplasms	36	26	38
Total animals with benign neoplasms	11	16	18
Total benign neoplasms	12	17	22
Total animals with malignant neoplasms	20	8	15
Total malignant neoplasms	24	9	16
Total animals with metastatic neoplasms	4	1	4
Total metastatic neoplasms	5	1	11
Total animals with malignant neoplasms, uncertain primary site	1		

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.
[b] Number of animals with any tissue examined microscopically
[c] Primary tumors: all tumors except metastatic tumors

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Talc: 0 mg/m³

Number of Days on Study	0	4	4	4	4	5	5	5	5	5	5	5	6	6	6	7	7	7	7	7	7	7
	0	3	3	8	8	1	4	7	7	8	8	8	2	7	8	1	3	3	3	3	3	3
	8	2	7	4	6	8	3	1	9	5	7	7	9	7	4	0	6	6	6	6	6	6
Carcass ID Number	4	3	4	5	3	3	4	4	5	3	4	5	5	4	4	5	3	3	3	3	3	3
	3	9	5	1	7	7	9	0	1	9	8	1	2	9	5	1	6	6	6	7	7	7
	5	1	4	2	4	2	4	5	5	5	9	8	3	3	5	7	1	4	7	0	1	5
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Alimentary System																						
Esophagus	M	M	+	M	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	M	M	M	A	A	A	A	M	+	+	A	A	+	+	A	M	+	M	+	+	+
Intestine large	A	+	A	A	A	A	A	A	A	+	+	A	+	+	+	A	+	+	+	+	+	+
Intestine large, cecum	A	+	A	A	A	A	A	A	A	+	A	A	A	+	+	A	+	+	+	+	+	+
Intestine large, colon	A	+	A	A	A	A	A	A	A	+	+	A	+	+	+	A	+	+	+	+	+	+
Intestine large, rectum	A	+	A	A	A	A	A	A	A	+	A	A	M	M	+	A	+	+	+	+	+	+
Intestine small	A	+	A	A	A	A	A	A	A	+	A	A	A	+	+	A	+	+	+	+	+	+
Intestine small, duodenum	A	A	A	A	A	A	A	A	A	+	A	A	A	+	+	A	+	+	+	+	+	+
Intestine small, ileum	A	+	A	A	A	A	A	A	A	+	A	A	A	A	+	A	+	+	+	+	+	+
Intestine small, jejunum	A	+	A	A	A	A	A	A	A	+	A	A	A	A	+	A	+	+	+	+	+	+
Liver	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																X						
Hemangiosarcoma, metastatic, spleen																						
Hepatocellular carcinoma								X	X			X				X	X	X				
Hepatocellular adenoma																						
Hepatocellular adenoma, multiple																						
Pancreas	M	+	+	+	+	A	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver												X										
Salivary glands	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	+	+	+	+	+	+	I	+	+	M	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	+	A	+	A	M	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																						
Heart	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																						
Adrenal gland	A	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+
Spindle cell, adenoma																						
Adrenal gland, cortex	A	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+
Adrenal gland, medulla	A	+	+	+	M	M	+	+	+	+	+	+	I	+	+	+	M	+	+	+	+	M
Pheochromocytoma malignant																						
Islets, pancreatic	M	+	I	+	+	M	+	A	+	M	+	A	+	I	M	I	+	+	+	+	+	M
Parathyroid gland	M	M	M	+	M	M	M	+	+	+	+	+	+	M	+	+	+	M	M	M	+	M
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X										
Thyroid gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+: Tissue examined microscopically
A: Autolysis precludes examination

M: Missing tissue
I: Insufficient tissue

X: Lesion present
Blank: Not examined

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Talc: 0 mg/m³ (continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	4	4	4	4	4	4	4	
	6	7	7	7	7	7	7	8	8	8	8	8	8	9	9	9	9	0	0	0	0	0	0	0	
Carcass ID Number	3	3	4	4	4	4	4	4	4	4	4	4	4	4	4	4	5	3	4	4	4	4	5	5	**Total**
	9	9	0	0	2	2	2	3	3	5	5	5	6	8	8	9	1	9	2	2	8	8	2	2	**Tissues/**
	2	8	2	3	1	3	4	1	4	1	2	8	4	5	8	2	3	3	6	7	2	4	0	1	**Tumors**
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Gallbladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	31
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	36
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	34
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	36
Intestine large, rectum	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	32
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	34
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	32
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Intestine small, jejunum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	32
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Hemangiosarcoma																									1
Hemangiosarcoma, metastatic, spleen								X																	1
Hepatocellular carcinoma																									6
Hepatocellular adenoma															X										1
Hepatocellular adenoma, multiple					X								X												2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Hepatocellular carcinoma, metastatic, liver																									1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	1	39
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Spindle cell, adenoma																						X			1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Pheochromocytoma malignant																					X				1
Islets, pancreatic	+	+	+	+	+	M	I	I	+	+	+	+	M	I	I	M	+	I	+	+	I	+	M	+	26
Parathyroid gland	+	+	M	+	+	+	M	+	+	+	M	M	+	+	+	M	M	M	M	M	+	+	+	M	25
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	44
Adenoma																									1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Talc: 0 mg/m³ (continued)

Number of Days on Study	0	4	4	4	4	5	5	5	5	5	5	5	6	6	6	7	7	7	7	7	7	7
	0	3	3	8	8	1	4	7	7	8	8	8	2	7	8	1	3	3	3	3	3	3
	8	2	7	4	6	8	3	1	9	5	7	7	9	7	4	0	6	6	6	6	6	6
Carcass ID Number	4	3	4	5	3	3	4	4	5	3	4	5	5	4	4	5	3	3	3	3	3	3
	3	9	5	1	7	7	9	0	1	9	8	1	2	9	5	1	6	6	6	7	7	7
	5	1	4	2	4	2	4	5	5	5	9	8	3	3	5	7	1	4	7	0	1	5
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
General Body System																						
None																						
Genital System																						
Epididymis	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	M	I
Preputial gland			+								+	+		+			+					
Prostate	M	+	M	M	+	I	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	A	+	M	+	+	+	+	+	A	A	+	+	A	+	+	+	+	+	+
Testes	A	+	+	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																						
Hematopoietic System																						
Bone marrow	A	+	A	+	+	A	+	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen																						
Lymph node	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	M	M	+	I	+	+	M	+	+	+	+	I	I	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	M	M	M	M	+	M	+	M	M	M	M	M	M	+	M	M	M	+	M	M	+	+
Lymph node, mediastinal	M	M	M	M	I	M	+	M	M	+	M	M	M	M	M	M	M	M	M	M	M	+
Lymph node, mesenteric	M	+	A	M	+	M	+	M	+	+	M	A	+	+	+	+	+	+	+	+	I	M
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																						
Thymus	M	I	M	M	+	M	M	A	+	M	+	+	+	I	+	+	M	+	+	+	+	+
Integumentary System																						
Mammary gland	M	M	M	M	M	M	M	+	M	+	M	I	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Musculoskeletal System																						
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																						
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Talc: 0 mg/m³ (continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	4	4	4	4	4	4	4	
	6	7	7	7	7	7	7	8	8	8	8	8	8	9	9	9	9	0	0	0	0	0	0	0	
Carcass ID Number	3	3	4	4	4	4	4	4	4	4	4	4	4	4	4	4	5	3	4	4	4	4	5	5	**Total Tissues/ Tumors**
	9	9	0	0	2	2	2	3	3	5	5	5	6	8	8	9	1	9	2	2	8	8	2	2	
	2	8	2	3	1	3	4	1	4	1	2	8	4	5	8	2	3	3	6	7	2	4	0	1	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	39
Preputial gland																					+	+	+		8
Prostate	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Hemangiosarcoma																		X							1
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Hemangiosarcoma, metastatic, spleen								X																	1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymph node, bronchial	I	+	M	+	+	+	+	M	+	+	+	+	+	+	M	+	M	+	+	M	+	+	M	M	32
Lymph node, mandibular	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	M	M	+	+	+	23
Lymph node, mediastinal	M	M	M	M	+	M	M	M	M	+	+	M	M	M	+	M	M	+	M	M	M	M	+	M	9
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	36
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	44
Hemangiosarcoma								X	X																2
Thymus	I	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	34
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	+	M	+	M	I	M	M	5
Skin	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Talc: 0 mg/m³ (continued)

Number of Days on Study	0	4	4	4	4	5	5	5	5	5	5	5	6	6	6	7	7	7	7	7	7	7
	0	3	3	8	8	1	4	7	7	8	8	8	2	7	8	1	3	3	3	3	3	3
	8	2	7	4	6	8	3	1	9	5	7	7	9	7	4	0	6	6	6	6	6	6
Carcass ID Number	4	3	4	5	3	3	4	4	5	3	4	5	5	4	4	5	3	3	3	3	3	3
	3	9	5	1	7	7	9	0	1	9	8	1	2	9	5	1	6	6	6	7	7	7
	5	1	4	2	4	2	4	5	5	5	9	8	3	3	5	7	1	4	7	0	1	5
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Respiratory System																						
Larynx	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	I	+	+
Lung	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																			X			
Alveolar/bronchiolar carcinoma																						
Alveolar/bronchiolar carcinoma, multiple																		X				
Hemangiosarcoma, metastatic, liver																X						
Nose	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Special Senses System																						
Ear																						
Harderian gland																						
Adenoma																						
Urinary System																						
Kidney	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uncertain primary site									X													
Urinary bladder	A	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma												X										
Systemic Lesions																						
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																						
Lymphoma malignant undifferentiated cell type																						

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Talc: 0 mg/m³ (continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	4	4	4	4	4	4	4	
	6	7	7	7	7	7	7	8	8	8	8	8	8	9	9	9	9	0	0	0	0	0	0	0	
Carcass ID Number	3	3	4	4	4	4	4	4	4	4	4	4	4	4	4	4	5	3	4	4	4	4	5	5	**Total**
	9	9	0	0	2	2	2	3	3	5	5	5	6	8	8	9	1	9	2	2	8	8	2	2	**Tissues/**
	2	8	2	3	1	3	4	1	4	1	2	8	4	5	8	2	3	3	6	7	2	4	0	1	**Tumors**
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Respiratory System																									
Larynx	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Alveolar/bronchiolar adenoma				X	X		X				X	X													6
Alveolar/bronchiolar carcinoma	X		X	X															X		X			X	6
Alveolar/bronchiolar carcinoma, multiple																									1
Hemangiosarcoma, metastatic, liver																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Trachea	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Special Senses System																									
Ear																					+				1
Harderian gland																		+							1
Adenoma																		X							1
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Carcinoma, metastatic, uncertain primary site																									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Sarcoma																									1
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymphoma malignant mixed											X						X								2
Lymphoma malignant undifferentiated cell type			X							X					X										3

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Talc: 6 mg/m^3

Number of Days on Study	2	2	3	4	5	5	5	5	5	5	6	6	6	6	6	6	7	7	7	7	7	7	7
	5	5	4	2	4	5	5	8	9	9	2	2	3	8	8	8	1	1	2	3	3	3	3
	3	3	4	3	6	0	8	4	0	1	4	6	3	1	5	8	0	9	2	6	6	6	6
Carcass ID Number	0	1	0	0	1	1	0	1	1	1	0	0	0	1	1	0	0	1	1	0	0	0	0
	3	3	4	0	2	6	4	5	5	2	4	7	3	5	0	6	1	5	3	0	0	0	0
	5	3	2	7	1	4	0	1	6	9	1	4	8	7	0	1	5	4	2	1	4	5	8
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Alimentary System																							
Esophagus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	M	I	M	A	A	A	A	+	A	+	I	A	A	A	+	A	A	M	+	+	+	+
Intestine large	A	+	+	A	A	A	A	A	+	A	+	+	A	+	A	+	+	+	+	+	+	+	+
Intestine large, cecum	A	A	+	A	A	A	A	A	+	A	+	A	A	+	A	+	A	+	+	+	+	+	+
Intestine large, colon	A	+	+	A	A	A	A	A	+	A	+	+	A	+	A	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	A	A	A	M	A	+	A	+	A	A	+	A	+	+	M	+	+	+	+	+
Intestine small	A	A	+	A	A	A	A	A	+	A	+	A	A	+	A	+	A	+	A	+	+	+	+
Intestine small, duodenum	A	A	+	A	A	A	A	A	A	A	+	A	A	A	A	+	A	+	A	+	+	+	M
Intestine small, ileum	A	A	A	A	A	A	A	A	+	A	+	A	A	A	A	+	A	+	A	+	+	+	+
Adenocarcinoma																							
Intestine small, jejunum	A	A	+	A	A	A	A	A	+	A	+	A	A	+	A	+	A	A	A	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma					X		X						X					X					
Hepatocellular adenoma													X				X					X	
Hepatocellular adenoma, multiple																							
Pancreas	M	A	+	A	M	A	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Salivary glands	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	A	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	A	+	A	A	+	+	+	+	I	A	+	+	+	+	+	I	+	+	+	+
Stomach, glandular	+	+	+	A	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Tooth		+																					
Cardiovascular System																							
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																							
Adrenal gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spindle cell, adenoma																							
Adrenal gland, cortex	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																							
Adrenal gland, medulla	A	+	+	+	+	+	+	+	+	+	+	I	+	+	M	+	+	+	+	M	M	+	+
Islets, pancreatic	M	A	M	A	M	A	M	M	+	+	+	+	M	+	I	M	+	+	+	+	M	+	M
Parathyroid gland	M	M	M	+	+	I	M	M	M	M	+	+	M	M	+	+	+	+	M	M	+	M	M
Pituitary gland	+	+	I	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars intermedia, adenoma														X									
Thyroid gland	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Talc: 6 mg/m³ (continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	4	4	4	4	4	4	
	6	6	7	7	7	7	7	7	7	8	8	8	8	8	8	9	9	9	0	0	0	0	0	0	
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	0	1	1	1	1	**Total**
	1	1	3	3	6	6	6	7	7	9	9	9	9	0	0	2	3	5	3	9	2	2	5	6	**Tissues/**
	0	4	3	6	4	5	6	1	2	3	5	6	9	1	5	7	5	5	2	2	4	5	8	2	**Tumors**
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Gallbladder	+	+	+	+	+	+	I	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	29
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	35
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Intestine large, rectum	+	+	+	I	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	32
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	34
Intestine small, duodenum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	30
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	32
Adenocarcinoma						X																			1
Intestine small, jejunum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	31
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hepatocellular carcinoma		X																							5
Hepatocellular adenoma	X								X											X	X	X			8
Hepatocellular adenoma, multiple																X									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	39
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Tooth															+						+				3
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	46
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Spindle cell, adenoma										X															1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma											X														1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	I	+	+	M	+	+	+	+	+	+	+	+	M	+	39
Islets, pancreatic	I	M	+	I	+	I	+	I	+	I	I	M	I	I	I	+	+	+	M	I	+	I	+	+	20
Parathyroid gland	M	M	M	+	+	I	M	I	M	+	M	+	+	M	M	+	+	M	+	M	+	+	+	+	21
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	44
Pars intermedia, adenoma														X											2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46

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Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Talc: 6 mg/m³ (continued)

Number of Days on Study	2	2	3	4	5	5	5	5	5	5	6	6	6	6	6	6	7	7	7	7	7	7	7
	5	5	4	2	4	5	5	8	9	9	2	2	3	8	8	8	1	1	2	3	3	3	3
	3	3	4	3	6	0	8	4	0	1	4	6	3	1	5	8	0	9	2	6	6	6	6
Carcass ID Number	0	1	0	0	1	1	0	1	1	1	0	0	0	1	1	0	0	1	1	0	0	0	0
	3	3	4	0	2	6	4	5	5	2	4	7	3	5	0	6	1	5	3	0	0	0	0
	5	3	2	7	1	4	0	1	6	9	1	4	8	7	0	1	5	4	2	1	4	5	8
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
General Body System																							
Tissue NOS	+	+	+																				
Genital System																							
Epididymis	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Preputial gland		+	+							+												+	
Prostate	+	+	M	A	I	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	A	+	+	A	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Testes	A	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Hematopoietic System																							
Bone marrow	+	+	+	+	A	A	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Lymph node, bronchial	+	+	+	+	M	+	I	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+
Lymph node, mandibular	M	M	+	M	M	+	+	+	+	M	+	M	M	M	+	M	+	+	+	+	M	M	M
Lymph node, mediastinal	M	M	M	M	M	+	M	M	M	+	M	M	M	M	M	M	M	M	+	+	M	M	M
Lymph node, mesenteric	M	M	M	M	+	M	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	M	+
Spleen	A	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	A	M	M	M	+	+	+	I	+	+	M	+	M	+	I	M	+	+	+	+	+	+	+
Integumentary System																							
Mammary gland	M	M	M	M	M	A	M	M	M	M	M	M	M	M	M	+	M	+	+	M	+	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																							
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																							
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																							
Larynx	A	+	+	A	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	I	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																				X			
Alveolar/bronchiolar carcinoma							X																
Hepatocellular carcinoma, metastatic, liver																		X					
Nose	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	A	I	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Talc: 6 mg/m³ (continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	3	3	3	3	3	3	-3	3	3	3	3	3	3	3	3	3	3	3	4	4	4	4	4	4	
	6	6	7	7	7	7	7	7	7	8	8	8	8	8	8	9	9	9	0	0	0	0	0	0	
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	0	1	1	1	1	**Total**
	1	1	3	3	6	6	6	7	7	9	9	9	9	0	0	2	3	5	3	9	2	2	5	6	**Tissues/**
	0	4	3	6	4	5	6	1	2	3	5	6	9	1	5	7	5	5	2	2	4	5	8	2	**Tumors**
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
General Body System																									
Tissue NOS																									3
Genital System																									
Epididymis	M	+	+	+	+	+	+	M	+	+	+	+	I	+	+	+	+	I	I	+	+	+	I	+	39
Preputial gland																		+		+					6
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph node, bronchial	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	M	39
Lymph node, mandibular	+	M	+	+	M	+	M	M	M	+	M	+	M	+	+	+	M	M	+	M	+	+	M	M	23
Lymph node, mediastinal	M	M	M	+	M	M	+	M	M	M	M	+	M	M	+	M	M	M	+	M	M	M	M	+	10
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Thymus	+	+	+	+	I	+	+	+	M	+	I	+	+	+	+	M	+	+	+	+	+	+	+	I	33
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	5
Skin	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	45
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Alveolar/bronchiolar adenoma		X						X						X											4
Alveolar/bronchiolar carcinoma														X											2
Hepatocellular carcinoma, metastatic, liver																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	43

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Talc: 6 mg/m³ (continued)

Number of Days on Study	253	253	344	423	546	550	558	584	590	591	624	626	633	681	685	688	710	719	722	736	736	736	736
Carcass ID Number	0351	1331	0421	0071	1211	1641	0401	1511	1561	1291	0411	0741	0381	1571	1001	0611	0151	1541	1321	0011	0041	0051	0081
Special Senses System																							
None																							
Urinary System																							
Kidney	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A	+	+	A	+	A	A	A	+	+	+	+	A	+	A	+	A	+	+	+	+	+	+
Systemic Lesions																							
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																				X			

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Talc: 6 mg/m³ (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	4	4	4	4	4	4	
	6	6	7	7	7	7	7	7	7	8	8	8	8	8	8	9	9	9	0	0	0	0	0	0	
	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	0	1	1	1	1	**Total**
Carcass ID Number	1	1	3	3	6	6	6	7	7	9	9	9	9	0	0	2	3	5	3	9	2	2	5	6	**Tissues/**
	0	4	3	6	4	5	6	1	2	3	5	6	9	1	5	7	5	5	2	2	4	5	8	2	**Tumors**
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	38
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant lymphocytic																									1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Talc: 18 mg/m³

Number of Days on Study	0	1	1	1	4	4	4	4	5	5	5	5	6	7	7	7	7	7	7	7	7	7	7	7
	2	1	1	5	2	3	5	7	3	4	5	5	7	2	2	2	2	3	3	3	3	3	3	3
	8	4	5	9	2	8	7	8	8	1	4	8	2	1	4	5	7	6	6	6	6	6	6	6
Carcass ID Number	1	1	1	3	2	1	2	2	1	2	2	2	2	2	2	3	3	1	1	1	1	2	2	2
	8	8	9	1	8	8	2	1	8	7	4	8	4	8	1	0	4	8	8	9	9	1	1	1
	7	3	5	0	5	6	1	9	5	7	9	3	1	2	5	6	3	4	9	2	3	1	3	4
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Alimentary System																								
Esophagus	M	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Gallbladder	M	A	A	A	M	A	+	A	+	A	A	M	A	+	A	+	A	+	+	+	+	+	+	+
Intestine large	A	+	+	+	A	+	+	A	+	A	A	A	+	A	A	+	A	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	A	A	A	+	A	+	A	A	A	A	A	A	+	A	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	A	A	+	+	A	+	A	A	A	+	A	A	+	A	+	+	+	+	+	+	+
Intestine large, rectum	A	+	M	+	A	M	+	M	I	A	A	A	+	A	A	+	A	+	M	+	+	+	+	+
Intestine small	A	A	+	A	A	A	+	A	+	A	A	A	A	A	A	+	A	+	+	+	+	+	+	+
Intestine small, duodenum	A	A	+	A	A	M	+	A	M	A	A	A	A	A	A	+	A	+	+	+	+	+	+	+
Intestine small, ileum	A	A	A	A	A	A	+	A	+	A	A	A	A	A	A	+	A	+	+	+	+	+	+	+
Intestine small, jejunum	A	A	+	A	A	A	+	A	+	A	A	A	A	A	A	+	A	+	+	+	+	+	+	+
Liver	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																							X	
Hepatocellular carcinoma						X	X		X	X	X	X									X			
Hepatocellular adenoma													•X						X	X				
Pancreas	+	+	+	+	A	+	+	+	M	A	A	A	+	A	+	+	+	+	+	+	+	+	I	+
Salivary glands	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	A	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	A	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	A	+	+	+	+	A	A	A	+	A	+	+	A	+	+	+	+	+	+	+
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung						X																		
Endocrine System																								
Adrenal gland	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Spindle cell, adenoma																	X							
Adrenal gland, cortex	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Adrenal gland, medulla	+	+	I	+	A	+	+	+	M	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	I	I	+	+	A	+	+	+	M	A	A	A	+	A	+	+	+	I	I	I	M	+	I	I
Parathyroid gland	+	+	+	+	A	M	M	+	I	M	A	+	+	M	+	M	+	+	+	I	M	M	+	M
Pituitary gland	+	+	+	+	A	+	+	+	+	+	A	+	+	M	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	A	I	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																								
General Body System																								
Tissue NOS															+									
Hemangioma																								
Hemangiosarcoma, metastatic, spleen															X									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Talc: 18 mg/m³ (continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	4	4	4	4	4	4	
	7	7	7	7	7	7	7	8	8	8	8	8	9	9	9	9	9	9	9	0	0	0	0	0	0	
Carcass ID Number	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	2	2	2	3	3	3	**Total**
	2	2	4	4	5	5	5	7	8	0	0	0	3	3	3	3	3	3	4	1	5	5	0	1	1	**Tissues/**
	3	4	2	8	0	1	2	9	4	3	4	8	2	3	4	7	8	9	5	7	3	5	7	1	3	**Tumors**
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	35
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	37
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Intestine large, rectum	M	I	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	31
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	36
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	34
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	35
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	36
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																										1
Hepatocellular carcinoma				X	X			X																X		11
Hepatocellular adenoma																								X		4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spindle cell, adenoma																										1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma																				X						1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	42
Islets, pancreatic	+	I	+	+	+	+	M	M	M	M	+	I	+	+	+	+	I	M	+	I	+	+	I	I	+	24
Parathyroid gland	+	+	+	+	M	+	M	M	+	M	M	M	+	M	+	+	+	M	+	+	+	M	M	M	+	26
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	45
Follicular cell, adenoma													X									X				2
General Body System																										
Tissue NOS																									+	2
Hemangioma																									X	1
Hemangiosarcoma, metastatic, spleen																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Talc: 18 mg/m³ (continued)

Number of Days on Study	0	1	1	1	4	4	4	4	5	5	5	6	6	7	7	7	7	7	7	7	7	7	7	7
	2	1	1	5	2	3	5	7	3	4	5	5	7	2	2	2	2	3	3	3	3	3	3	3
	8	4	5	9	2	8	7	8	8	1	4	8	2	1	4	5	7	6	6	6	6	6	6	6
Carcass ID Number	1	1	1	3	2	1	2	2	1	2	2	2	2	2	2	3	3	1	1	1	1	2	2	2
	8	8	9	1	8	8	2	1	8	7	4	8	4	8	1	0	4	8	8	9	9	1	1	1
	7	3	5	0	5	6	1	9	5	7	9	3	1	2	5	6	3	4	9	2	3	1	3	4
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Genital System																								
Epididymis	+	+	+	+	A	+	+	+	+	+	M	+	+	A	+	+	+	+	+	+	M	+	+	+
Preputial gland		+	+	+			+																	
Prostate	+	M	M	M	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	M	M	M	A	+	+	+	+	A	A	A	M	A	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	A	+	+	+	+	+	A	M	+	A	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																								
Bone marrow	+	+	+	+	A	A	+	+	A	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	+	+	M	M	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung						X																		
Lymph node, mandibular	M	I	I	+	A	M	+	M	+	M	M	M	M	M	+	+	+	+	+	+	M	M	M	M
Hemangiosarcoma, metastatic, spleen															X									
Lymph node, mediastinal	M	M	M	M	M	M	M	M	M	M	M	M	+	M	+	M	M	+	M	M	M	M	M	M
Lymph node, mesenteric	M	+	+	M	A	+	+	M	+	+	A	+	+	A	+	+	M	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen															X									
Spleen	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma													X		X									
Thymus	+	M	+	M	M	+	+	+	+	+	A	+	M	+	+	+	+	+	+	+	M	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung						X																		
Integumentary System																								
Mammary gland	I	I	M	M	M	M	M	+	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen															X									
Skeletal muscle						+																		
Thoracic, alveolar/bronchiolar carcinoma, metastatic, lung						X																		
Nervous System																								
Brain	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Talc: 18 mg/m³ (continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	4	4	4	4	4	4	
	7	7	7	7	7	7	7	8	8	8	8	8	9	9	9	9	9	9	9	0	0	0	0	0	0	
Carcass ID Number	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	2	2	2	3	3	3	**Total**
	2	2	4	4	5	5	5	7	8	0	0	0	3	3	3	3	3	3	4	1	5	5	0	1	1	**Tissues/**
	3	4	2	8	0	1	2	9	4	3	4	8	2	3	4	7	8	9	5	7	3	5	7	1	3	**Tumors**
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	M	+	42
Preputial gland						+					+						+	+								8
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	39
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	44
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Lymph node, mandibular	+	M	I	M	+	M	+	+	M	M	M	+	+	M	+	M	M	+	M	M	+	M	M	M	+	19
Hemangiosarcoma, metastatic, spleen																										1
Lymph node, mediastinal	+	M	M	M	M	M	M	+	M	M	M	M	M	M	M	+	M	M	M	M	+	M	M	M	M	7
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	I	+	+	+	+	40
Hemangiosarcoma, metastatic, spleen																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangiosarcoma																										2
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	I	+	+	+	+	+	+	+	40
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Integumentary System																										
Mammary gland	+	M	I	M	+	+	I	+	M	M	M	M	+	M	M	M	M	M	M	M	M	+	M	M	M	8
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma, metastatic, spleen																										1
Skeletal muscle																										1
Thoracic, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Talc: 18 mg/m³ (continued)

Number of Days on Study	028	114	115	159	422	438	457	478	538	541	554	558	672	721	724	725	727	736	736	736	736	736	736	736
Carcass ID Number	1871	1831	1951	3101	2851	1861	2211	2191	1851	2771	2491	2831	2411	2821	2151	3061	3431	1841	1891	1921	1931	2111	2131	2141
Respiratory System																								
Larynx	+	+	+	+	A	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X						X					
Alveolar/bronchiolar adenoma, multiple																		X						
Alveolar/bronchiolar carcinoma						X											X							
Hemangiosarcoma, metastatic, spleen															X									
Hepatocellular carcinoma, metastatic, liver										X		X												
Nose	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	A	+	+	A	+	+	A	M	+	A	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Harderian gland																+				+				
Adenoma																X				X				
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	A	+	+	+	+	+	A	A	+	A	A	+	A	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Talc: 18 mg/m³ (continued)

Number of Days on Study	737	737	737	737	737	737	737	738	738	738	738	738	739	739	739	739	739	739	739	740	740	740	740	740	740	
Carcass ID Number	2231	2241	2421	2481	2501	2511	2521	2791	2841	3031	3041	3081	3321	3331	3341	3371	3381	3391	3451	2171	2531	2551	3071	3111	3131	**Total Tissues/ Tumors**
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar adenoma											X						X		X		X			X		7
Alveolar/bronchiolar adenoma, multiple				X																						2
Alveolar/bronchiolar carcinoma																										2
Hemangiosarcoma, metastatic, spleen																										1
Hepatocellular carcinoma, metastatic, liver																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Trachea	+	+	+	+	+	I	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Special Senses System																										
Harderian gland					+	+																				4
Adenoma					X	X																				4
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Talc

	0 mg/m^3	6 mg/m^3	18 mg/m^3
Harderian Gland: Adenoma			
Overall rates[a]	1/46 (2%)	0/47 (0%)	4/49 (8%)
Adjusted rates[b]	3.3%	0.0%	12.0%
Terminal rates[c]	1/30 (3%)	0/28 (0%)	3/32 (9%)
First incidence (days)	736 (T)	–[e]	725
Life table tests[d]	P=0.073	P=0.514N	P=0.204
Logistic regression tests[d]	P=0.075	P=0.514N	P=0.216
Cochran-Armitage test[d]	P=0.065		
Fisher exact test[d]		P=0.495N	P=0.201
Liver: Hepatocellular Adenoma			
Overall rates	3/45 (7%)	9/47 (19%)	4/48 (8%)
Adjusted rates	10.0%	29.5%	11.8%
Terminal rates	3/30 (10%)	7/28 (25%)	3/32 (9%)
First incidence (days)	736 (T)	633	672
Life table tests	P=0.489N	P=0.050	P=0.539
Logistic regression tests	P=0.493N	P=0.061	P=0.552
Cochran-Armitage test	P=0.515N		
Fisher exact test		P=0.070	P=0.536
Liver: Hepatocellular Carcinoma			
Overall rates	6/45 (13%)	5/47 (11%)	11/48 (23%)
Adjusted rates	16.7%	13.7%	27.3%
Terminal rates	2/30 (7%)	1/28 (4%)	5/32 (16%)
First incidence (days)	571	546	438
Life table tests	P=0.114	P=0.491N	P=0.187
Logistic regression tests	P=0.116	P=0.445N	P=0.203
Cochran-Armitage test	P=0.097		
Fisher exact test		P=0.469N	P=0.177
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rates	9/45 (20%)	13/47 (28%)	14/48 (29%)
Adjusted rates	25.6%	38.1%	34.5%
Terminal rates	5/30 (17%)	8/28 (29%)	7/32 (22%)
First incidence (days)	571	546	438
Life table tests	P=0.256	P=0.228	P=0.230
Logistic regression tests	P=0.216	P=0.257	P=0.223
Cochran-Armitage test	P=0.225		
Fisher exact test		P=0.269	P=0.217
Lung: Alveolar/bronchiolar Adenoma			
Overall rates	6/45 (13%)	4/47 (9%)	9/48 (19%)
Adjusted rates	20.0%	14.3%	27.0%
Terminal rates	6/30 (20%)	4/28 (14%)	8/32 (25%)
First incidence (days)	736 (T)	736 (T)	672
Life table tests	P=0.224	P=0.411N	P=0.333
Logistic regression tests	P=0.251	P=0.411N	P=0.371
Cochran-Armitage test	P=0.210		
Fisher exact test		P=0.342N	P=0.336

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Talc (continued)

	0 mg/m³	6 mg/m³	18 mg/m³
Lung: Alveolar/bronchiolar Carcinoma			
Overall rates	7/45 (16%)	2/47 (4%)	2/48 (4%)
Adjusted rates	23.3%	5.9%	5.2%
Terminal rates	7/30 (23%)	1/28 (4%)	0/32 (0%)
First incidence (days)	736 (T)	558	438
Life table tests	P=0.068N	P=0.093N	P=0.068N
Logistic regression tests	P=0.069N	P=0.073N	P=0.070N
Cochran-Armitage test	P=0.065N		
Fisher exact test		P=0.069N	P=0.065N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rates	12/45 (27%)	5/47 (11%)	11/48 (23%)
Adjusted rates	40.0%	16.4%	30.8%
Terminal rates	12/30 (40%)	4/28 (14%)	8/32 (25%)
First incidence (days)	736 (T)	558	438
Life table tests	P=0.533N	P=0.063N	P=0.426N
Logistic regression tests	P=0.552N	P=0.043N	P=0.423N
Cochran-Armitage test	P=0.554N		
Fisher exact test		P=0.043N	P=0.429N
Pituitary Gland (Pars Intermedia): Adenoma			
Overall rates	0/44 (0%)	2/44 (5%)	0/46 (0%)
Adjusted rates	0.0%	6.5%	0.0%
Terminal rates	0/29 (0%)	1/27 (4%)	0/32 (0%)
First incidence (days)	-	681	-
Life table tests	P=0.547N	P=0.238	-f
Logistic regression tests	P=0.566N	P=0.239	-
Cochran-Armitage test	P=0.564N		
Fisher exact test		P=0.247	-
Spleen: Hemangiosarcoma			
Overall rates	2/44 (5%)	0/44 (0%)	2/47 (4%)
Adjusted rates	6.9%	0.0%	5.5%
Terminal rates	2/29 (7%)	0/28 (0%)	0/32 (0%)
First incidence (days)	736 (T)	-	672
Life table tests	P=0.595	P=0.246N	P=0.650N
Logistic regression tests	P=0.581	P=0.246N	P=0.668N
Cochran-Armitage test	P=0.577		
Fisher exact test		P=0.247N	P=0.666N
All Organs: Hemangiosarcoma			
Overall rates	4/46 (9%)	0/47 (0%)	3/49 (6%)
Adjusted rates	12.9%	0.0%	8.4%
Terminal rates	3/30 (10%)	0/28 (0%)	1/32 (3%)
First incidence (days)	710	-	672
Life table tests	P=0.529N	P=0.071N	P=0.448N
Logistic regression tests	P=0.545N	P=0.060N	P=0.456N
Cochran-Armitage test	P=0.554N		
Fisher exact test		P=0.056N	P=0.464N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Talc (continued)

	0 mg/m³	6 mg/m³	18 mg/m³
All Organs: Hemangioma or Hemangiosarcoma			
Overall rates	4/46 (9%)	0/47 (0%)	4/49 (8%)
Adjusted rates	12.9%	0.0%	11.4%
Terminal rates	3/30 (10%)	0/28 (0%)	2/32 (6%)
First incidence (days)	710	–	672
Life table tests	P=0.515	P=0.071N	P=0.590N
Logistic regression tests	P=0.505	P=0.060N	P=0.598N
Cochran-Armitage test	P=0.492		
Fisher exact test		P=0.056N	P=0.607N
All Organs: Malignant Lymphoma (Lymphocytic, Mixed, or Undifferentiated Cell Type)			
Overall rates	5/46 (11%)	1/47 (2%)	0/49 (0%)
Adjusted rates	16.7%	3.6%	0.0%
Terminal rates	5/30 (17%)	1/28 (4%)	0/32 (0%)
First incidence (days)	736 (T)	736 (T)	–
Life table tests	P=0.019N	P=0.116N	P=0.027N
Logistic regression tests	P=0.019N	P=0.116N	P=0.027N
Cochran-Armitage test	P=0.020N		
Fisher exact test		P=0.097N	P=0.024N
All Organs: Benign Tumors			
Overall rates	11/46 (24%)	16/47 (34%)	18/49 (37%)
Adjusted rates	35.2%	51.1%	51.4%
Terminal rates	10/30 (33%)	13/28 (46%)	15/32 (47%)
First incidence (days)	587	633	672
Life table tests	P=0.158	P=0.135	P=0.127
Logistic regression tests	P=0.154	P=0.188	P=0.138
Cochran-Armitage test	P=0.139		
Fisher exact test		P=0.199	P=0.128
All Organs: Malignant Tumors			
Overall rates	20/46 (43%)	8/47 (17%)	15/49 (31%)
Adjusted rates	58.3%	23.3%	35.9%
Terminal rates	16/30 (53%)	4/28 (14%)	6/32 (19%)
First incidence (days)	571	546	438
Life table tests	P=0.253N	P=0.012N	P=0.166N
Logistic regression tests	P=0.262N	P=0.005N	P=0.152N
Cochran-Armitage test	P=0.245N		
Fisher exact test		P=0.005N	P=0.139N
All Organs: Benign or Malignant Tumors			
Overall rates	26/46 (57%)	20/47 (43%)	28/49 (57%)
Adjusted rates	76.2%	58.0%	66.5%
Terminal rates	22/30 (73%)	14/28 (50%)	18/32 (56%)
First incidence (days)	571	546	438
Life table tests	P=0.442	P=0.208N	P=0.554
Logistic regression tests	P=0.344	P=0.102N	P=0.503
Cochran-Armitage test	P=0.399		
Fisher exact test		P=0.127N	P=0.558

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Talc (continued)

(T)Terminal sacrifice
a Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
b Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
c Observed incidence at terminal kill
d Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
e Not applicable; no tumors in animal group
f Value of statistic cannot be computed.

Table C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Talc[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Moribund	1	2	3
Natural deaths	16	18	14
Survivors			
Terminal sacrifice	30	28	32
Missexed	1	1	0
Missing	2	1	1
Animals examined microscopically	46	47	49
Alimentary System			
Gallbladder	(31)	(29)	(35)
Dilatation			1 (3%)
Epithelium, hyperplasia, papillary			1 (3%)
Intestine large, cecum	(34)	(35)	(37)
Hyperplasia, lymphoid		1 (3%)	3 (8%)
Intestine large, colon	(36)	(38)	(39)
Hyperplasia, lymphoid	1 (3%)		
Intestine large, rectum	(32)	(32)	(31)
Serosa, inflammation, suppurative		1 (3%)	
Intestine small, duodenum	(32)	(30)	(34)
Hyperplasia, lymphoid			1 (3%)
Mucosa, atrophy	3 (9%)	7 (23%)	3 (9%)
Intestine small, ileum	(33)	(32)	(35)
Hyperplasia, lymphoid	5 (15%)	3 (9%)	5 (14%)
Mucosa, atrophy	3 (9%)	5 (16%)	4 (11%)
Peyer's patch, necrosis	1 (3%)		
Intestine small, jejunum	(32)	(31)	(36)
Hyperplasia, lymphoid			1 (3%)
Mucosa, atrophy	3 (9%)	3 (10%)	2 (6%)
Liver	(45)	(47)	(48)
Abscess	1 (2%)		1 (2%)
Focal cellular change	4 (9%)	3 (6%)	5 (10%)
Hematocyst		1 (2%)	
Hematopoietic cell proliferation	2 (4%)	2 (4%)	
Infarct	2 (4%)		
Inflammation, focal		3 (6%)	1 (2%)
Mineralization, focal		1 (2%)	
Necrosis, focal	4 (9%)	5 (11%)	4 (8%)
Pigmentation, hemosiderin, focal			1 (2%)
Bile duct, hyperplasia, focal			1 (2%)
Serosa, inflammation, suppurative			1 (2%)
Pancreas	(42)	(39)	(42)
Serosa, inflammation, suppurative			1 (2%)
Stomach, forestomach	(43)	(41)	(46)
Hyperplasia, squamous, focal		1 (2%)	1 (2%)
Tooth		(3)	
Dysplasia		3 (100%)	
Cardiovascular System			
Heart	(45)	(46)	(49)
Thrombosis		1 (2%)	1 (2%)
Coronary artery, mineralization		1 (2%)	
Myocardium, degeneration, focal	1 (2%)		
Myocardium, fibrosis, focal		1 (2%)	

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Talc (continued)

	0 mg/m^3	6 mg/m^3	18 mg/m^3
Endocrine System			
Adrenal gland	(43)	(46)	(47)
Spindle cell, hyperplasia	38 (88%)	37 (80%)	35 (74%)
Adrenal gland, cortex	(43)	(46)	(47)
Atrophy	1 (2%)		
Hyperplasia, focal		1 (2%)	
Vacuolization cytoplasmic, focal		3 (7%)	4 (9%)
Parathyroid gland	(25)	(21)	(26)
Cyst	3 (12%)	1 (5%)	
Pituitary gland	(44)	(44)	(46)
Cyst	1 (2%)		1 (2%)
Pigmentation, lipofuscin	1 (2%)		
Thyroid gland	(45)	(46)	(45)
Cyst	2 (4%)	1 (2%)	1 (2%)
Follicular cell, hyperplasia	4 (9%)	8 (17%)	8 (18%)
General Body System			
None			
Genital System			
Epididymis	(39)	(39)	(42)
Inflammation, suppurative	1 (3%)	1 (3%)	
Preputial gland	(8)	(6)	(8)
Dilatation	7 (88%)	6 (100%)	8 (100%)
Inflammation	3 (38%)		1 (13%)
Prostate	(40)	(43)	(44)
Inflammation, suppurative	3 (8%)	7 (16%)	4 (9%)
Epithelium, hyperplasia		1 (2%)	
Seminal vesicle	(41)	(43)	(39)
Inflammation, suppurative		2 (5%)	1 (3%)
Testes	(43)	(44)	(45)
Aspermatogenesis, diffuse			1 (2%)
Atrophy, diffuse			1 (2%)
Hypospermia	1 (2%)	2 (5%)	
Inflammation, suppurative		1 (2%)	
Seminiferous tubule, degeneration, focal	3 (7%)	4 (9%)	1 (2%)
Hematopoietic System			
Bone marrow	(40)	(42)	(43)
Hyperplasia	4 (10%)	1 (2%)	1 (2%)
Myelofibrosis	2 (5%)	2 (5%)	
Myeloid cell, hyperplasia	4 (10%)	7 (17%)	1 (2%)
Lymph node	(45)	(46)	(48)
Iliac, hyperplasia, lymphoid	1 (2%)		
Iliac, hyperplasia, plasma cell	1 (2%)		
Lumbar, hyperplasia, lymphoid	1 (2%)	1 (2%)	
Lumbar, hyperplasia, plasma cell		1 (2%)	
Pancreatic, inflammation, granulomatous		1 (2%)	
Renal, depletion lymphoid			1 (2%)
Renal, hyperplasia, lymphoid			1 (2%)

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Talc (continued)

	0 mg/m³	6 mg/m³	18 mg/m³
Hematopoietic System (continued)			
Lymph node, bronchial	(32)	(39)	(44)
Abscess			1 (2%)
Hyperplasia, histiocytic	1 (3%)	32 (82%)	42 (95%)
Hyperplasia, histiocytic, lymphoid		1 (3%)	
Hyperplasia, lymphoid	3 (9%)	10 (26%)	23 (52%)
Infiltration cellular, mixed cell	3 (9%)	1 (3%)	3 (7%)
Inflammation, acute	1 (3%)		
Follicular, necrosis	1 (3%)		
Lymph node, mandibular	(23)	(23)	(19)
Hyperplasia, histiocytic		1 (4%)	
Hyperplasia, lymphoid			1 (5%)
Follicular, necrosis			1 (5%)
Lymph node, mediastinal	(9)	(10)	(7)
Hyperplasia, histiocytic	1 (11%)	1 (10%)	2 (29%)
Hyperplasia, lymphoid		2 (20%)	
Lymph node, mesenteric	(36)	(39)	(40)
Depletion lymphoid	1 (3%)		2 (5%)
Hyperplasia, lymphoid	4 (11%)	3 (8%)	6 (15%)
Infiltration cellular, mixed cell	18 (50%)	20 (51%)	13 (33%)
Inflammation, granulomatous		1 (3%)	
Thrombosis			1 (3%)
Follicular, necrosis		6 (15%)	2 (5%)
Spleen	(44)	(44)	(47)
Hematocyst		1 (2%)	
Hematopoietic cell proliferation	6 (14%)	7 (16%)	10 (21%)
Hyperplasia, lymphoid	3 (7%)	2 (5%)	3 (6%)
Hyperplasia, mast cell			1 (2%)
Inflammation, granulomatous		1 (2%)	
Lymphoid follicle, depletion lymphoid		2 (5%)	5 (11%)
Lymphoid follicle, necrosis	2 (5%)	5 (11%)	1 (2%)
Thymus	(34)	(33)	(40)
Cyst	3 (9%)	2 (6%)	1 (3%)
Hyperplasia, lymphoid			1 (3%)
Inflammation, granulomatous		1 (3%)	
Necrosis	1 (3%)		2 (5%)
Cortex, depletion lymphoid	6 (18%)	10 (30%)	8 (20%)
Epithelial cell, hyperplasia, focal	1 (3%)		
Integumentary System			
Skin	(44)	(45)	(48)
Abscess		1 (2%)	
Alopecia	1 (2%)		1 (2%)
Inflammation, acute		2 (4%)	
Ulcer, focal		2 (4%)	
Musculoskeletal System			
Bone	(46)	(47)	(49)
Rib, cartilage, fracture healed	1 (2%)		
Nervous System			
Brain	(46)	(47)	(48)
Mineralization, focal	37 (80%)	39 (83%)	38 (79%)

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Talc (continued)

	0 mg/m³	6 mg/m³	18 mg/m³
Respiratory System			
Larynx	(42)	(41)	(46)
Inflammation, acute	1 (2%)		1 (2%)
Lung	(45)	(47)	(48)
Congestion	3 (7%)	1 (2%)	1 (2%)
Hyperplasia, macrophage	3 (7%)	46 (98%)	48 (100%)
Inflammation, chronic active		16 (34%)	40 (83%)
Thrombosis			1 (2%)
Alveolar epithelium, hyperplasia, focal	1 (2%)		
Peribronchiolar, inflammation, chronic active		1 (2%)	
Perivascular, inflammation, suppurative	1 (2%)		
Nose	(45)	(46)	(47)
Cytoplasmic alteration, focal	5 (11%)	23 (50%)	40 (85%)
Erosion, focal	1 (2%)	1 (2%)	2 (4%)
Inflammation, acute	4 (9%)	4 (9%)	7 (15%)
Special Senses System			
Ear	(1)		
Inflammation, granulomatous	1 (100%)		
Urinary System			
Kidney	(45)	(46)	(48)
Casts protein	1 (2%)		
Cyst	2 (4%)		
Hydronephrosis	3 (7%)	1 (2%)	
Inflammation, suppurative, focal	3 (7%)	5 (11%)	3 (6%)
Metaplasia, osseous, focal		3 (7%)	
Nephropathy, chronic	3 (7%)		2 (4%)
Capsule, inflammation, suppurative			1 (2%)
Pelvis, inflammation, suppurative	2 (4%)	5 (11%)	1 (2%)
Urinary bladder	(43)	(38)	(43)
Dysplasia, focal	1 (2%)		
Inflammation, chronic active	6 (14%)	5 (13%)	2 (5%)
Ulcer, focal			1 (2%)
Transitional epithelium, hyperplasia		1 (3%)	

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.

APPENDIX D
SUMMARY LESIONS IN FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF TALC

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Talc[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Moribund	2	4	4
Natural deaths	17	21	21
Survivors			
Terminal sacrifice	30	23	25
Missing	1	1	
Culled		1	
Animals examined microscopically	46	48	50
Alimentary System			
Esophagus	(43)	(47)	(48)
Gallbladder	(31)	(28)	(29)
Intestine large, cecum	(35)	(29)	(34)
Leiomyoma			1 (3%)
Intestine large, colon	(38)	(33)	(32)
Leiomyosarcoma		1 (3%)	
Intestine small, ileum	(33)	(27)	(31)
Liver	(46)	(46)	(50)
Hemangioma		1 (2%)	
Hepatocellular carcinoma	7 (15%)	5 (11%)	4 (8%)
Hepatocellular adenoma	5 (11%)	1 (2%)	4 (8%)
Mesentery	(2)		–
Pancreas	(42)	(39)	(44)
Salivary glands	(46)	(48)	(50)
Hemangioma	1 (2%)		
Stomach, glandular	(45)	(39)	(46)
Cardiovascular System			
Heart	(46)	(48)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)	
Endocrine System			
Adrenal gland	(46)	(45)	(50)
Spindle cell, adenoma	1 (2%)		
Adrenal gland, cortex	(46)	(44)	(50)
Adenoma	1 (2%)		
Adrenal gland, medulla	(41)	(43)	(45)
Pheochromocytoma malignant	1 (2%)		
Pituitary gland	(42)	(42)	(48)
Adenoma	5 (12%)	4 (10%)	2 (4%)
Carcinoma		2 (5%)	
Thyroid gland	(43)	(47)	(49)
Follicular cell, adenoma	1 (2%)	2 (4%)	2 (4%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Talc (continued)

	0 mg/m³	6 mg/m³	18 mg/m³
General Body System			
Tissue NOS	(4)	(1)	(2)
Fibrosarcoma	1 (25%)		
Hemangioma	1 (25%)		1 (50%)
Hemangiosarcoma			1 (50%)
Genital System			
Ovary	(38)	(43)	(46)
Adenocarcinoma, metastatic, uterus	1 (3%)		
Adenoma	1 (3%)	1 (2%)	
Cystadenoma		1 (2%)	
Luteoma	2 (5%)		
Uterus	(44)	(45)	(49)
Adenocarcinoma	1 (2%)		
Carcinoma adenosquamous			1 (2%)
Hematopoietic System			
Bone marrow	(41)	(43)	(45)
Lymph node	(46)	(46)	(49)
Lymph node, bronchial	(38)	(37)	(43)
Adenocarcinoma, metastatic, kidney		1 (3%)	
Adenocarcinoma, metastatic, uterus	1 (3%)		
Alveolar/bronchiolar carcinoma, metastatic, lung		3 (8%)	
Lymph node, mandibular	(35)	(38)	(36)
Lymph node, mediastinal	(13)	(17)	(14)
Adenocarcinoma, metastatic, kidney		1 (6%)	
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (6%)	
Lymph node, mesenteric	(35)	(31)	(37)
Spleen	(45)	(44)	(50)
Hemangiosarcoma			1 (2%)
Thymus	(40)	(40)	(41)
Alveolar/bronchiolar carcinoma, metastatic, lung		2 (5%)	
Integumentary System			
Mammary gland	(41)	(45)	(48)
Fibrosarcoma			1 (2%)
Musculoskeletal System			
Bone	(46)	(48)	(50)
Vertebra, alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)	
Nervous System			
Spinal cord			(1)
Thoracic, ganglioneuroma			1 (100%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Talc (continued)

	0 mg/m³	6 mg/m³	18 mg/m³
Respiratory System			
Lung	(46)	(48)	(50)
Adenocarcinoma, metastatic, kidney		1 (2%)	
Alveolar/bronchiolar adenoma	3 (7%)	2 (4%)	2 (4%)
Alveolar/bronchiolar carcinoma	2 (4%)	4 (8%)	1 (2%)
Hemangiosarcoma, metastatic, tissue NOS			1 (2%)
Hepatocellular carcinoma, metastatic, liver	2 (4%)	2 (4%)	
Trachea	(40)	(36)	(45)
Special Senses System			
Harderian gland	(2)	(2)	(1)
Adenocarcinoma			1 (100%)
Adenoma	2 (100%)	1 (50%)	
Urinary System			
Kidney	(46)	(46)	(50)
Adenocarcinoma		1 (2%)	
Hepatocellular carcinoma, metastatic, liver	1 (2%)		
Urinary bladder	(44)	(40)	(41)
Systemic Lesions			
Multiple organs[b]	(46)	(48)	(50)
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant lymphocytic	2 (4%)	3 (6%)	3 (6%)
Lymphoma malignant mixed	3 (7%)	4 (8%)	2 (4%)
Lymphoma malignant undifferentiated cell	2 (4%)		2 (4%)
Tumor Summary			
Total animals with primary neoplasms[c]	31	26	21
Total primary neoplasms	42	33	31
Total animals with benign neoplasms	18	9	10
Total benign neoplasms	23	13	13
Total animals with malignant neoplasms	19	19	15
Total malignant neoplasms	19	20	18
Total animals with metastatic neoplasms	3	5	1
Total metastatic neoplasms	5	13	1

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.
[b] Number of animals with any tissue examined microscopically
[c] Primary tumors: all tumors except metastatic tumors

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Talc: 0 mg/m³

Number of Days on Study	0	4	4	4	5	5	5	5	5	5	6	6	6	6	6	7	7	7	7	7	7
	3	2	6	8	0	0	0	4	5	9	4	8	8	8	9	2	2	2	2	2	2
	0	6	5	7	5	6	9	4	2	8	1	0	3	6	2	3	9	9	9	9	9
Carcass ID Number	5	5	5	3	4	4	3	4	4	4	5	5	4	5	4	4	3	3	3	3	3
	3	0	3	7	1	2	8	1	7	7	0	2	9	0	4	9	7	8	8	8	8
	3	0	4	6	7	0	2	5	5	3	5	8	7	7	6	6	7	1	4	6	9
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Alimentary System																					
Esophagus	+	+	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	M	A	M	A	M	A	+	A	A	A	A	A	+	A	A	+	+	+	+	+
Intestine large	A	+	+	A	A	A	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	A	A	A	A	A	A	A	+	A	+	A	+	A	+	+	+	+	+	+
Intestine large, colon	A	+	A	A	A	A	+	+	A	+	A	+	+	+	+	+	+	M	+	+	+
Intestine large, rectum	A	M	+	M	M	A	+	+	M	A	A	M	+	+	+	+	+	+	+	+	M
Intestine small	A	+	A	A	A	A	A	+	A	A	A	A	A	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	A	A	A	A	A	A	A	A	A	A	A	+	+	A	+	+	+	+	M
Intestine small, ileum	A	+	A	A	A	A	A	A	A	A	A	A	A	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	A	A	A	A	A	+	A	A	A	A	A	+	A	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma		X				X					X			X							X
Hepatocellular adenoma																					X
Mesentery							+														
Pancreas	+	+	A	+	A	A	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																					
Stomach	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																					
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																					
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spindle cell, adenoma																					
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					
Adrenal gland, medulla	+	+	+	+	M	+	M	+	+	+	I	I	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																					
Islets, pancreatic	+	+	M	+	A	A	M	+	I	M	I	M	I	M	+	+	+	+	+	+	+
Parathyroid gland	M	M	+	M	+	+	M	+	M	I	+	M	+	+	+	M	M	M	I	M	+
Pituitary gland	M	+	+	+	M	M	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+
Adenoma													X		X	X					X
Thyroid gland	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																					

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Talc: 0 mg/m³ (continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	9	0	0	0	0	0	0	0	1	1	1	1	1	1	2	2	2	2	2	3	3	3	3	3	3	
Carcass ID Number	3	4	4	4	4	4	4	4	4	4	4	4	4	4	5	5	5	5	5	4	4	5	5	5	5	**Total**
	9	1	1	4	4	4	4	5	7	7	7	7	7	7	0	0	0	0	2	0	8	3	3	3	3	**Tissues/**
	0	1	8	0	1	2	3	5	0	0	1	4	8	9	1	2	4	9	9	9	0	0	1	8	9	**Tumors**
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Gallbladder	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	31
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	35
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	34
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	35
Intestine small, duodenum	+	M	M	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	27
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	33
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Hepatocellular carcinoma	X																						X			7
Hepatocellular adenoma						X		X			X													X		5
Mesentery													+													2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Hemangioma												X														1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Spindle cell, adenoma																				X						1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma	X																									1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	41
Pheochromocytoma malignant												X														1
Islets, pancreatic	+	+	M	+	I	+	I	+	I	I	+	I	I	+	+	+	+	M	I	+	I	+	+	M	+	25
Parathyroid gland	+	+	+	M	+	+	M	+	I	+	M	+	M	M	+	+	I	M	+	+	+	M	M	M	+	23
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Adenoma																									X	5
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	43
Follicular cell, adenoma																						X				1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Talc: 0 mg/m³ (continued)

Number of Days on Study	030	426	465	487	505	506	509	544	552	598	641	680	683	686	692	723	729	729	729	729	729
Carcass ID Number	5331	5001	5341	3761	4171	4201	3821	4151	4751	4731	5051	5281	4971	5071	4461	4961	3771	3811	3841	3861	3891
General Body System																					
Tissue NOS																					
Fibrosarcoma																					
Hemangioma																					
Genital System																					
Ovary	+	+	+	+	+	+	+	I	+	+	I	M	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus																					
Adenoma																					
Luteoma																					
Uterus	M	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																					
Hematopoietic System																					
Bone marrow	+	+	A	+	A	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	M	+	+	+	+	M	+	M	M	+	+	+	M	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus																					
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	M	M	+
Lymph node, mediastinal	M	M	+	M	M	M	+	M	+	M	M	M	+	M	+	+	M	M	+	M	+
Lymph node, mesenteric	M	+	+	M	M	M	+	M	M	+	+	+	+	I	+	+	+	M	+	+	+
Spleen	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	M	+	+	+	M	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+
Integumentary System																					
Mammary gland	A	+	+	+	+	A	+	I	+	+	+	M	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																					
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																					
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Talc: 0 mg/m³ (continued)

Number of Days on Study	729	730	730	730	730	730	730	730	731	731	731	731	731	731	732	732	732	732	732	733	733	733	733	733	733	
Carcass ID Number	3901	4111	4181	4401	4411	4421	4431	4451	4501	4701	4711	4741	4781	4791	5011	5021	5041	5091	5291	4091	4801	5301	5311	5381	5391	**Total Tissues/ Tumors**
General Body System																										
Tissue NOS									+		+		+						+							4
Fibrosarcoma									X																	1
Hemangioma																			X							1
Genital System																										
Ovary	+	+	+	M	+	+	+	M	+	+	+	M	+	+	M	+	+	+	+	I	+	+	+	+	+	38
Adenocarcinoma, metastatic, uterus							X																			1
Adenoma																	X									1
Luteoma						X											X									2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenocarcinoma							X																			1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph node, bronchial	M	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	38
Adenocarcinoma, metastatic, uterus							X																			1
Lymph node, mandibular	+	+	+	+	M	M	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	M	+	+	+	35
Lymph node, mediastinal	M	M	M	M	M	+	M	M	M	M	+	+	M	M	M	M	M	M	M	+	M	M	M	M	+	13
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	35
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	40
Integumentary System																										
Mammary gland	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Talc: 0 mg/m³ (continued)

Number of Days on Study	0	4	4	4	5	5	5	5	5	5	6	6	6	6	6	7	7	7	7	7	7
	3	2	6	8	0	0	0	4	5	9	4	8	8	8	9	2	2	2	2	2	2
	0	6	5	7	5	6	9	4	2	8	1	0	3	6	2	3	9	9	9	9	9
Carcass ID Number	5	5	5	3	4	4	3	4	4	4	5	5	4	5	4	4	3	3	3	3	3
	3	0	3	7	1	2	8	1	7	7	0	2	9	0	4	9	7	8	8	8	8
	3	0	4	6	7	0	2	5	5	3	5	8	7	7	6	6	7	1	4	6	9
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Respiratory System																					
Larynx	+	+	+	+	+	A	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																	X				
Alveolar/bronchiolar carcinoma																			X		
Hepatocellular carcinoma, metastatic, liver						X								X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	A	+	A	+	M	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																					
Harderian gland																		+			
Adenoma																		X			
Urinary System																					
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver						X															
Urinary bladder	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																					
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic							X														
Lymphoma malignant mixed																					
Lymphoma malignant undifferentiated cell type															X						

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Talc: 0 mg/m^3 (continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	9	0	0	0	0	0	0	0	1	1	1	1	1	1	2	2	2	2	2	3	3	3	3	3	3	
Carcass ID Number	3	4	4	4	4	4	4	4	4	4	4	4	4	4	5	5	5	5	5	4	4	5	5	5	5	**Total**
	9	1	1	4	4	4	4	4	5	7	7	7	7	7	0	0	0	0	2	0	8	3	3	3	3	**Tissues/**
	0	1	8	0	1	2	3	5	0	0	1	4	8	9	1	2	4	9	9	9	0	0	1	8	9	**Tumors**
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	I	+	+	+	+	+	+	+	+	+	42
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Alveolar/bronchiolar adenoma						X															X					3
Alveolar/bronchiolar carcinoma																						X				2
Hepatocellular carcinoma, metastatic, liver																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	40
Special Senses System																										
Harderian gland																									+	2
Adenoma																									X	2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Hepatocellular carcinoma, metastatic, liver																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymphoma malignant lymphocytic																X										2
Lymphoma malignant mixed													X					X							X	3
Lymphoma malignant undifferentiated cell type			X																							2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Talc: 6 mg/m³

Number of Days on Study	0	0	4	4	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	7	7	7
	2	9	2	9	0	3	4	5	5	6	1	2	2	4	4	6	7	7	8	9	9	0	0	1
	0	2	2	1	0	4	8	4	9	4	8	1	8	1	5	5	6	8	6	2	9	9	9	2
Carcass ID Number	1	0	0	1	0	1	1	1	0	1	0	1	0	0	1	1	0	1	1	0	0	1	1	0
	1	5	1	1	5	4	7	4	1	7	2	2	5	8	3	0	5	7	3	8	6	1	4	2
	7	5	6	5	0	7	6	8	9	5	2	0	6	1	6	8	8	1	9	3	0	8	0	0
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Alimentary System																								
Esophagus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	M	M	M	A	A	+	+	+	A	A	A	A	A	A	A	A	A	M	A	A	+	A	+
Intestine large	A	+	A	A	A	+	A	+	+	A	+	+	A	A	A	+	A	+	A	+	A	+	A	+
Intestine large, cecum	A	A	A	A	A	A	A	+	+	A	A	+	A	A	A	+	A	A	A	A	A	+	A	+
Intestine large, colon	A	A	A	A	A	+	A	+	+	A	+	+	A	A	A	+	A	+	A	+	A	+	A	+
Leiomyosarcoma																								
Intestine large, rectum	A	+	A	A	A	M	M	I	M	A	+	M	M	A	A	M	A	+	A	A	A	+	A	+
Intestine small	A	A	A	A	A	A	A	+	+	A	A	+	A	A	A	+	A	A	A	A	A	+	A	+
Intestine small, duodenum	A	A	A	A	A	A	A	+	+	A	A	+	A	A	A	A	A	A	A	A	A	+	A	+
Intestine small, ileum	A	A	A	A	A	A	A	+	+	A	A	+	A	A	A	A	A	A	A	A	A	+	A	+
Intestine small, jejunum	A	A	A	A	A	A	A	+	+	A	A	+	A	A	A	+	A	A	A	A	A	+	A	+
Liver	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Hemangioma																								
Hepatocellular carcinoma															X				X					
Hepatocellular adenoma																								
Pancreas	+	+	+	A	A	+	+	+	+	+	+	+	I	M	+	+	A	+	A	+	A	+	+	I
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Stomach, glandular	A	+	+	A	A	+	+	+	+	A	A	+	+	A	+	+	A	+	+	+	+	+	A	+
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung				X																				
Endocrine System																								
Adrenal gland	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	A	+	+	+	+	+	+	+	+	M	+	+	+	A	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Islets, pancreatic	M	I	+	A	A	I	I	+	+	M	I	M	M	M	+	+	A	+	M	I	M	M	I	I
Parathyroid gland	I	+	+	A	M	M	+	+	M	M	M	+	+	M	+	+	M	M	I	+	M	I	+	M
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	M	+	+	M	I	+	+	+
Adenoma																								
Carcinoma						X												X						
Thyroid gland	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Talc: 6 mg/m³ (continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	1	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	4	9	9	9	9	0	0	0	0	0	1	1	1	1	1	2	2	2	2	2	2	3	3	3	
Carcass ID Number	0	0	0	0	1	0	0	0	0	1	0	0	1	1	1	1	1	1	1	1	1	0	1	1	**Total**
	8	2	2	3	0	5	5	7	7	0	8	8	0	1	3	4	4	6	6	6	7	4	7	8	**Tissues/**
	5	4	9	0	6	2	4	6	8	7	7	9	9	1	8	4	5	6	8	9	2	7	8	0	**Tumors**
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Gallbladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	28
Intestine large	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	34
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	29
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Leiomyosarcoma																			X						1
Intestine large, rectum	A	+	+	M	+	+	+	+	+	+	M	I	+	+	+	+	+	+	+	M	+	+	+	M	23
Intestine small	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	29
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	M	M	25
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	27
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	28
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Hemangioma								X																	1
Hepatocellular carcinoma														X			X							X	5
Hepatocellular adenoma								X																	1
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Stomach, forestomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar carcinoma, metastatic, lung																									1
Endocrine System																									
Adrenal gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adrenal gland, cortex	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adrenal gland, medulla	A	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	I	+	+	+	+	+	+	43
Islets, pancreatic	A	I	+	M	I	+	I	+	M	I	+	+	I	+	I	I	+	+	+	+	+	+	+	+	20
Parathyroid gland	M	M	I	I	+	M	+	+	M	M	M	+	M	+	M	M	I	M	M	+	I	+	M	+	18
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	42
Adenoma					X						X	X								X					4
Carcinoma																									2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Follicular cell, adenoma					X															X					2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Talc: 6 mg/m³ (continued)

Number of Days on Study	0	0	4	4	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	7	7	7
	2	9	2	9	0	3	4	5	5	6	1	2	2	4	4	6	7	7	8	9	9	0	0	1
	0	2	2	1	0	4	8	4	9	4	8	1	8	1	5	5	6	8	6	2	9	9	9	2
Carcass ID Number	1	0	0	1	0	1	1	1	0	1	0	1	0	0	1	1	0	1	1	0	0	1	1	0
	1	5	1	1	5	4	7	4	1	7	2	2	5	8	3	0	5	7	3	8	6	1	4	2
	7	5	6	5	0	7	6	8	9	5	2	0	6	1	6	8	8	1	9	3	0	8	0	0
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
General Body System																								
Tissue NOS																								
Genital System																								
Ovary	+	+	+	A	+	+	+	+	+	+	+	+	M	+	+	+	A	+	+	+	+	+	+	+
Adenoma																								
Cystadenoma																								
Uterus	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+
Hematopoietic System																								
Bone marrow	+	+	+	A	+	+	A	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Lymph node	M	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	M	M	M	+	+	+	M	I	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+	I
Adenocarcinoma, metastatic, kidney															X									
Alveolar/bronchiolar carcinoma, metastatic, lung				X													X					X		
Lymph node, mandibular	M	+	M	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+
Lymph node, mediastinal	M	M	M	+	M	M	M	M	M	M	M	M	+	+	+	M	M	M	+	I	M	+	+	M
Adenocarcinoma, metastatic, kidney															X									
Alveolar/bronchiolar carcinoma, metastatic, lung																						X		
Lymph node, mesenteric	M	M	A	A	A	+	M	+	+	+	+	+	+	A	+	+	A	M	M	+	+	+	+	+
Spleen	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Thymus	M	M	+	+	+	I	+	+	+	+	I	+	+	+	+	+	M	M	M	+	I	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung				X																		X		
Integumentary System																								
Mammary gland	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Skin	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vertebra, alveolar/bronchiolar carcinoma, metastatic, lung																						X		
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Talc: 6 mg/m³ (continued)

Number of Days on Study	714	729	729	729	729	730	730	730	730	730	731	731	731	731	731	732	732	732	732	732	732	733	733	733	
Carcass ID Number	0851	0241	0291	0301	1061	0521	0541	0761	0781	1071	0871	0891	1091	1111	1381	1441	1451	1661	1681	1691	1721	0471	1781	1801	Total Tissues/ Tumors
General Body System																									
Tissue NOS			+																						1
Genital System																									
Ovary	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	43
Adenoma																X									1
Cystadenoma					X																				1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Hematopoietic System																									
Bone marrow	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph node, bronchial	+	+	I	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	37
Adenocarcinoma, metastatic, kidney																									1
Alveolar/bronchiolar carcinoma, metastatic, lung																									3
Lymph node, mandibular	M	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	38
Lymph node, mediastinal	M	M	+	M	M	+	M	+	+	+	+	+	+	+	M	M	M	M	M	+	M	M	M	M	17
Adenocarcinoma, metastatic, kidney																									1
Alveolar/bronchiolar carcinoma, metastatic, lung																									1
Lymph node, mesenteric	A	+	+	+	+	+	I	M	+	+	+	M	+	I	+	+	M	+	+	M	+	+	+	+	31
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Alveolar/bronchiolar carcinoma, metastatic, lung																									2
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Vertebra, alveolar/bronchiolar carcinoma, metastatic, lung																									1
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Talc: 6 mg/m³ (continued)

Number of Days on Study	0	0	4	4	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	7	7	7
	2	9	2	9	0	3	4	5	5	6	1	2	2	4	4	6	7	7	8	9	9	0	0	1
	0	2	2	1	0	4	8	4	9	4	8	1	8	1	5	5	6	8	6	2	9	9	9	2
Carcass ID Number	1	0	0	1	0	1	1	1	0	1	0	1	0	0	1	1	0	1	1	0	0	1	1	0
	1	5	1	1	5	4	7	4	1	7	2	2	5	8	3	0	5	7	3	8	6	1	4	2
	7	5	6	5	0	7	6	8	9	5	2	0	6	1	6	8	8	1	9	3	0	8	0	0
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Respiratory System																								
Larynx	+	+	+	A	A	I	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, kidney															X									
Alveolar/bronchiolar adenoma									X															
Alveolar/bronchiolar carcinoma				X												X	X					X		
Hepatocellular carcinoma, metastatic, liver															X									
Nose	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	A	A	+	M	+	+	A	A	+	A	A	+	+	M	+	M	+	+	+	+	+
Special Senses System																								
Eye												+												
Harderian gland												+												
Adenoma																								
Urinary System																								
Kidney	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Adenocarcinoma															X									
Urinary bladder	A	A	+	A	+	+	+	+	+	A	+	+	+	A	A	+	A	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic													X										X	
Lymphoma malignant mixed																								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Talc: 6 mg/m³ (continued)

Number of Days on Study	714	729	729	729	729	730	730	730	730	730	731	731	731	731	731	732	732	732	732	732	732	733	733	733	
Carcass ID Number	0851	0241	0291	0301	1061	0521	0541	0761	0781	1071	0871	0891	1091	1111	1381	1441	1451	1661	1681	1691	1721	0471	1781	1801	**Total Tissues/ Tumors**
Respiratory System																									
Larynx	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma, metastatic, kidney																									1
Alveolar/bronchiolar adenoma							X																		2
Alveolar/bronchiolar carcinoma																									4
Hepatocellular carcinoma, metastatic, liver														X											2
Nose	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Trachea	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	36
Special Senses System																									
Eye																									1
Harderian gland													+												2
Adenoma													X												1
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenocarcinoma																									1
Urinary bladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant lymphocytic												X													3
Lymphoma malignant mixed			X					X	X	X															4

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Talc: 18 mg/m³

Number of Days on Study	020	028	028	028	028	028	028	473	508	516	548	554	558	569	581	642	646	655	661	665	686	692	706	716	718
Carcass ID Number	2921	1961	2011	2031	2041	2061	2071	3491	3461	2021	2391	3161	3531	3601	2701	3281	2321	3521	2271	2281	2361	2661	2961	2671	2591
Alimentary System																									
Esophagus	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	M	M	A	A	A	M	M	+	M	A	A	A	A	+	A	A	+	A	A	A	+	+	A	+
Intestine large	A	A	A	+	+	A	A	+	+	A	+	A	+	A	+	A	+	A	A	A	+	+	A	A	+
Intestine large, cecum	A	A	A	+	A	A	A	+	+	A	+	A	A	A	+	A	+	A	A	A	+	+	A	A	+
Leiomyoma																									
Intestine large, colon	A	A	A	+	A	A	A	I	+	A	+	A	A	A	+	A	A	A	A	A	+	+	A	A	+
Intestine large, rectum	A	A	A	+	+	A	A	M	I	M	M	A	+	A	+	A	+	M	A	M	+	+	M	A	+
Intestine small	A	A	A	+	A	A	A	+	+	A	+	A	+	A	+	A	+	A	A	A	A	+	A	A	+
Intestine small, duodenum	A	A	A	+	A	A	A	+	+	A	M	A	A	A	+	A	A	A	A	A	A	+	A	A	+
Intestine small, ileum	A	A	A	A	A	A	A	+	A	A	+	A	A	A	+	A	+	A	A	A	A	+	A	A	+
Intestine small, jejunum	A	A	A	+	A	A	A	+	A	A	A	A	+	A	+	A	A	A	A	A	A	+	A	A	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									X
Hepatocellular adenoma															X										X
Pancreas	A	+	+	+	M	A	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	A	+	+	A	I	+	+	+	+	A	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	I	I	M	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	A	+	+	I	M	A	M	+	+	M	M	+	+	I	I	M	+	+	+	M	I	I	+	A	+
Parathyroid gland	+	M	M	+	+	M	M	M	M	M	+	+	+	+	M	M	+	+	I	+	M	M	+	+	+
Pituitary gland	+	+	+	+	M	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																				X					
Thyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
Tissue NOS								+																	
Hemangioma																									
Hemangiosarcoma								X																	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Talc: 18 mg/m³ (continued)

Number of Days on Study	729	729	729	729	729	730	730	730	730	731	731	731	731	731	732	732	732	732	732	732	733	733	733	733	733	
Carcass ID Number	2101	2291	2341	2381	2401	2601	2611	2861	2881	2941	2981	2991	3171	3191	3241	3261	3291	3541	3551	3581	2561	2891	2901	3221	3591	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	29
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	36
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	34
Leiomyoma												X														1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	32
Intestine large, rectum	+	+	+	+	M	+	M	+	+	+	M	+	+	M	M	+	+	I	+	+	+	+	+	+	+	27
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	34
Intestine small, duodenum	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	27
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	31
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	31
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma	X										X			X												4
Hepatocellular adenoma									X													X				4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Islets, pancreatic	+	I	M	I	+	I	+	I	+	+	+	M	I	+	I	+	+	I	I	+	I	+	+	M	I	23
Parathyroid gland	M	I	+	+	+	I	M	M	M	+	I	+	+	M	M	+	+	M	I	M	+	+	+	M	+	25
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma	X																									2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma							X	X																		2
General Body System																										
Tissue NOS									+																	2
Hemangioma									X																	1
Hemangiosarcoma																										1

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Talc: 18 mg/m³ (continued)

Number of Days on Study	020	028	028	028	028	028	028	473	508	516	548	554	558	569	581	642	646	655	661	665	686	692	706	716	718
Carcass ID Number	2921	1961	2011	2031	2041	2061	2071	3491	3461	2021	2391	3161	3531	3601	2701	3281	2321	3521	2271	2281	2361	2661	2961	2671	2591
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	M	+	+	M	+	+	+	+
Uterus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma adenosquamous																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	A	+	A	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+
Lymph node	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	M	M	M	+	M	M	M	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	M	M	M	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	+	+	+	M	+	M	+	+
Lymph node, mesenteric	M	M	A	+	M	M	M	+	+	A	+	A	+	+	+	M	+	+	+	+	M	+	M	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	M	M	+	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	I
Integumentary System																									
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord																									
Thoracic, ganglioneuroma																									
Respiratory System																									
Larynx	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X														
Alveolar/bronchiolar carcinoma													X												
Hemangiosarcoma, metastatic, tissue NOS								X																	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	M	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Talc: 18 mg/m³ (continued)

Number of Days on Study	729	729	729	729	729	730	730	730	730	731	731	731	731	731	732	732	732	732	732	732	733	733	733	733	733	
Carcass ID Number	2101	2291	2341	2381	2401	2601	2611	2861	2881	2941	2981	2991	3171	3191	3241	3261	3291	3541	3551	3581	2561	2891	2901	3221	3591	**Total Tissues/ Tumors**
Genital System																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	46
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma adenosquamous																				X						1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Lymph node, mandibular	M	+	+	M	I	M	+	+	M	+	+	+	+	+	M	M	+	+	+	+	+	M	+	M	+	36
Lymph node, mediastinal	M	M	M	M	M	M	M	M	+	M	+	+	M	+	M	M	M	M	M	+	M	+	+	M	M	14
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	37
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																	X									1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	41
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrosarcoma																X										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord	+																									1
Thoracic, ganglioneuroma	X																									1
Respiratory System																										
Larynx	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma												X														2
Alveolar/bronchiolar carcinoma																										1
Hemangiosarcoma, metastatic, tissue NOS																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	M	+	+	+	+	+	+	+	+	+	+	+	+	M	I	+	+	+	+	+	+	+	+	+	+	45

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Talc: 18 mg/m³ (continued)

Number of Days on Study	020	028	028	028	028	028	028	473	508	516	548	554	558	569	581	642	646	655	661	665	686	692	706	716	718
Carcass ID Number	2921	1961	2011	2031	2041	2061	2071	3491	3461	2021	2391	3161	3531	3601	2701	3281	2321	3521	2271	2281	2361	2661	2961	2671	2591
Special Senses System																									
Harderian gland																							+		
Adenocarcinoma																							X		
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A	A	+	+	+	+	A	+	+	+	+	A	+	+	+	A	+	A	+	+	A	+	A	A	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																X									
Lymphoma malignant lymphocytic																								X	
Lymphoma malignant mixed																									
Lymphoma malignant undifferentiated cell type																		X							

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Talc: 18 mg/m³ (continued)

Number of Days on Study	729	729	729	729	729	730	730	730	730	731	731	731	731	731	732	732	732	732	732	732	733	733	733	733	733	
Carcass ID Number	2101	2291	2341	2381	2401	2601	2611	2861	2881	2941	2981	2991	3171	3191	3241	3261	3291	3541	3551	3581	2561	2891	2901	3221	3591	**Total Tissues/ Tumors**
Special Senses System																										
Harderian gland																										1
Adenocarcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic												X		X			X									3
Lymphoma malignant mixed																						X				2
Lymphoma malignant undifferentiated cell type																				X						2

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Talc

	0 mg/m³	6 mg/m³	18 mg/m³
Liver: Hepatocellular Adenoma			
Overall rates[a]	5/46 (11%)	1/47 (2%)	4/50 (8%)
Adjusted rates[b]	16.7%	4.3%	14.0%
Terminal rates[c]	5/30 (17%)	1/23 (4%)	2/25 (8%)
First incidence (days)	729 (T)	729 (T)	581
Life table tests[d]	P=0.565	P=0.169N	P=0.602N
Logistic regression tests[d]	P=0.603N	P=0.169N	P=0.539N
Cochran-Armitage test[d]	P=0.523N		
Fisher exact test[d]		P=0.097N	P=0.447N
Liver: Hepatocellular Carcinoma			
Overall rates	7/46 (15%)	5/47 (11%)	4/50 (8%)
Adjusted rates	19.1%	18.4%	15.4%
Terminal rates	3/30 (10%)	3/23 (13%)	3/25 (12%)
First incidence (days)	426	645	718
Life table tests	P=0.308N	P=0.487N	P=0.344N
Logistic regression tests	P=0.243N	P=0.372N	P=0.255N
Cochran-Armitage test	P=0.197N		
Fisher exact test		P=0.364N	P=0.216N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rates	11/46 (24%)	6/47 (13%)	7/50 (14%)
Adjusted rates	31.1%	22.5%	25.2%
Terminal rates	7/30 (23%)	4/23 (17%)	5/25 (20%)
First incidence (days)	426	645	581
Life table tests	P=0.329N	P=0.262N	P=0.330N
Logistic regression tests	P=0.253N	P=0.147N	P=0.227N
Cochran-Armitage test	P=0.184N		
Fisher exact test		P=0.131N	P=0.163N
Lung: Alveolar/bronchiolar Adenoma			
Overall rates	3/46 (7%)	2/49 (4%)	2/50 (4%)
Adjusted rates	10.0%	6.7%	6.4%
Terminal rates	3/30 (10%)	1/23 (4%)	1/25 (4%)
First incidence (days)	729 (T)	559	548
Life table tests	P=0.505N	P=0.589N	P=0.562N
Logistic regression tests	P=0.467N	P=0.499N	P=0.515N
Cochran-Armitage test	P=0.425N		
Fisher exact test		P=0.470N	P=0.460N
Lung: Alveolar/bronchiolar Carcinoma			
Overall rates	2/46 (4%)	4/49 (8%)	1/50 (2%)
Adjusted rates	6.7%	11.6%	2.6%
Terminal rates	2/30 (7%)	0/23 (0%)	0/25 (0%)
First incidence (days)	729 (T)	491	558
Life table tests	P=0.383N	P=0.286	P=0.539N
Logistic regression tests	P=0.325N	P=0.356	P=0.500N
Cochran-Armitage test	P=0.309N		
Fisher exact test		P=0.369	P=0.468N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Talc (continued)

	0 mg/m³	6 mg/m³	18 mg/m³
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rates	5/46 (11%)	6/49 (12%)	3/50 (6%)
Adjusted rates	16.7%	17.5%	8.9%
Terminal rates	5/30 (17%)	1/23 (4%)	1/25 (4%)
First incidence (days)	729 (T)	491	548
Life table tests	P=0.337N	P=0.394	P=0.428N
Logistic regression tests	P=0.269N	P=0.519	P=0.367N
Cochran-Armitage test	P=0.235N		
Fisher exact test		P=0.545	P=0.311N
Ovary: Luteoma			
Overall rates	2/38 (5%)	0/43 (0%)	0/46 (0%)
Adjusted rates	8.0%	0.0%	0.0%
Terminal rates	2/25 (8%)	0/21 (0%)	0/24 (0%)
First incidence (days)	729 (T)	–[e]	–
Life table tests	P=0.177N	P=0.277N	P=0.246N
Logistic regression tests	P=0.177N	P=0.277N	P=0.246N
Cochran-Armitage test	P=0.146N		
Fisher exact test		P=0.217N	P=0.202N
Pituitary Gland (Unspecified Site): Adenoma			
Overall rates	5/42 (12%)	4/43 (9%)	2/48 (4%)
Adjusted rates	15.1%	18.2%	7.1%
Terminal rates	2/30 (7%)	4/22 (18%)	1/25 (4%)
First incidence (days)	683	729 (T)	665
Life table tests	P=0.239N	P=0.610	P=0.290N
Logistic regression tests	P=0.189N	P=0.604N	P=0.220N
Cochran-Armitage test	P=0.133N		
Fisher exact test		P=0.485N	P=0.166N
Pituitary Gland (Unspecified Site): Carcinoma			
Overall rates	0/42 (0%)	2/43 (5%)	0/48 (0%)
Adjusted rates	0.0%	5.5%	0.0%
Terminal rates	0/30 (0%)	0/22 (0%)	0/25 (0%)
First incidence (days)	–	534	–
Life table tests	P=0.591N	P=0.237	–[f]
Logistic regression tests	P=0.515N	P=0.274	–
Cochran-Armitage test	P=0.542N		
Fisher exact test		P=0.253	–
Pituitary Gland (Unspecified Site): Adenoma or Carcinoma			
Overall rates	5/42 (12%)	6/43 (14%)	2/48 (4%)
Adjusted rates	15.1%	22.7%	7.1%
Terminal rates	2/30 (7%)	4/22 (18%)	1/25 (4%)
First incidence (days)	683	534	665
Life table tests	P=0.216N	P=0.352	P=0.290N
Logistic regression tests	P=0.150N	P=0.451	P=0.220N
Cochran-Armitage test	P=0.111N		
Fisher exact test		P=0.517	P=0.166N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Talc (continued)

	0 mg/m³	6 mg/m³	18 mg/m³
All Organs: Hemangioma or Hemangiosarcoma			
Overall rates	2/46 (4%)	1/49 (2%)	3/50 (6%)
Adjusted rates	6.7%	4.3%	10.1%
Terminal rates	2/30 (7%)	1/23 (4%)	2/25 (8%)
First incidence (days)	729 (T)	729 (T)	473
Life table tests	P=0.323	P=0.593N	P=0.434
Logistic regression tests	P=0.356	P=0.593N	P=0.495
Cochran-Armitage test	P=0.399		
Fisher exact test		P=0.476N	P=0.540
All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, Mixed, or Undifferentiated Cell Type)			
Overall rates	7/46 (15%)	7/49 (14%)	8/50 (16%)
Adjusted rates	21.3%	26.7%	27.4%
Terminal rates	5/30 (17%)	5/23 (22%)	5/25 (20%)
First incidence (days)	509	628	642
Life table tests	P=0.358	P=0.454	P=0.387
Logistic regression tests	P=0.406	P=0.607	P=0.463
Cochran-Armitage test	P=0.514		
Fisher exact test		P=0.563N	P=0.571
All Organs: Benign Tumors			
Overall rates	18/46 (39%)	9/49 (18%)	10/50 (20%)
Adjusted rates	54.5%	36.4%	33.0%
Terminal rates	15/30 (50%)	8/23 (35%)	6/25 (24%)
First incidence (days)	683	559	548
Life table tests	P=0.148N	P=0.125N	P=0.145N
Logistic regression tests	P=0.094N	P=0.044N	P=0.071N
Cochran-Armitage test	P=0.050N		
Fisher exact test		P=0.022N	P=0.033N
All Organs: Malignant Tumors			
Overall rates	19/46 (41%)	19/49 (39%)	15/50 (30%)
Adjusted rates	51.9%	55.4%	45.6%
Terminal rates	13/30 (43%)	9/23 (39%)	8/25 (32%)
First incidence (days)	426	491	473
Life table tests	P=0.372N	P=0.340	P=0.441N
Logistic regression tests	P=0.241N	P=0.546N	P=0.279N
Cochran-Armitage test	P=0.143N		
Fisher exact test		P=0.483N	P=0.173N
All Organs: Benign or Malignant Tumors			
Overall rates	31/46 (67%)	26/49 (53%)	21/50 (42%)
Adjusted rates	81.4%	75.1%	58.9%
Terminal rates	23/30 (77%)	15/23 (65%)	11/25 (44%)
First incidence (days)	426	491	473
Life table tests	P=0.141N	P=0.537	P=0.168N
Logistic regression tests	P=0.036N	P=0.162N	P=0.035N
Cochran-Armitage test	P=0.011N		
Fisher exact test		P=0.112N	P=0.011N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Talc (continued)

(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no tumors in animal group
[f] Value of statistic cannot be computed.

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Talc[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Moribund	2	4	4
Natural deaths	17	21	21
Survivors			
Terminal sacrifice	30	23	25
Missing	1	1	
Culled		1	
Animals examined microscopically	46	48	50
Alimentary System			
Intestine large, cecum	(35)	(29)	(34)
Hyperplasia, lymphoid			1 (3%)
Serosa, inflammation, suppurative		1 (3%)	
Intestine large, colon	(38)	(33)	(32)
Serosa, inflammation, suppurative		2 (6%)	
Intestine small, duodenum	(27)	(25)	(27)
Ulcer, focal	1 (4%)		
Mucosa, atrophy	2 (7%)	6 (24%)	4 (15%)
Serosa, inflammation, suppurative		2 (8%)	
Intestine small, ileum	(33)	(27)	(31)
Hyperplasia, lymphoid	1 (3%)	1 (4%)	
Mucosa, atrophy	4 (12%)	6 (22%)	6 (19%)
Peyer's patch, necrosis			1 (3%)
Serosa, inflammation, suppurative		2 (7%)	1 (3%)
Intestine small, jejunum	(33)	(28)	(31)
Mucosa, atrophy	2 (6%)	7 (25%)	3 (10%)
Serosa, inflammation, suppurative		2 (7%)	1 (3%)
Liver	(46)	(46)	(50)
Eosinophilic focus		1 (2%)	
Fibrosis, focal		1 (2%)	
Focal cellular change	2 (4%)	3 (7%)	1 (2%)
Hematopoietic cell proliferation	1 (2%)	2 (4%)	2 (4%)
Inflammation, focal	1 (2%)	2 (4%)	1 (2%)
Necrosis, focal	1 (2%)	2 (4%)	2 (4%)
Pigmentation, hemosiderin, focal		1 (2%)	
Centrilobular, degeneration		1 (2%)	
Centrilobular, necrosis, coagulative		1 (2%)	
Serosa, inflammation, suppurative	4 (9%)	7 (15%)	5 (10%)
Sinusoid, inflammation	2 (4%)		
Pancreas	(42)	(39)	(44)
Inflammation, focal			2 (5%)
Acinus, hyperplasia, focal	1 (2%)		
Serosa, inflammation, suppurative	1 (2%)	5 (13%)	4 (9%)
Salivary glands	(46)	(48)	(50)
Inflammation, acute		1 (2%)	1 (2%)
Stomach	(45)	(45)	(50)
Serosa, inflammation, granulomatous			1 (2%)
Serosa, inflammation, suppurative	1 (2%)	2 (4%)	1 (2%)
Stomach, forestomach	(45)	(45)	(50)
Hyperplasia, mast cell, focal			1 (2%)
Hyperplasia, squamous, focal	2 (4%)	4 (9%)	2 (4%)
Ulcer, focal	1 (2%)	3 (7%)	

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Talc (continued)

	0 mg/m³	6 mg/m³	18 mg/m³
Alimentary System (continued)			
Stomach, glandular	(45)	(39)	(46)
Inflammation, suppurative			1 (2%)
Ulcer, focal	1 (2%)	1 (3%)	
Forestomach, inflammation, focal		1 (3%)	2 (4%)
Cardiovascular System			
Heart	(46)	(48)	(50)
Myocardium, degeneration, focal	1 (2%)		
Myocardium, inflammation, focal		1 (2%)	
Myocardium, mineralization, focal	1 (2%)		
Pericardium, inflammation, suppurative	1 (2%)	2 (4%)	4 (8%)
Endocrine System			
Adrenal gland	(46)	(45)	(50)
Capsule, inflammation, suppurative	4 (9%)	7 (16%)	5 (10%)
Corticomedullary junction, hemorrhage	2 (4%)	3 (7%)	1 (2%)
Spindle cell, hyperplasia	46 (100%)	45 (100%)	47 (94%)
Adrenal gland, cortex	(46)	(44)	(50)
Cyst	2 (4%)	3 (7%)	
Inflammation, suppurative, focal			1 (2%)
Vacuolization cytoplasmic, focal	3 (7%)		
Adrenal gland, medulla	(41)	(43)	(45)
Hyperplasia, focal	2 (5%)		
Parathyroid gland	(23)	(18)	(25)
Hyperplasia	1 (4%)		
Pituitary gland	(42)	(42)	(48)
Cyst	2 (5%)		
Hemorrhage, focal	2 (5%)		
Hyperplasia, focal	2 (5%)		
Pigmentation, lipofuscin	1 (2%)		
Thyroid gland	(43)	(47)	(49)
Cyst	2 (5%)		
Inflammation, acute, focal			2 (4%)
C-cell, hyperplasia	1 (2%)		1 (2%)
Follicular cell, hyperplasia	9 (21%)	12 (26%)	10 (20%)
General Body System			
Tissue NOS	(4)	(1)	(2)
Thrombosis, chronic	1 (25%)		
Genital System			
Ovary	(38)	(43)	(46)
Abscess	4 (11%)	10 (23%)	7 (15%)
Cyst	6 (16%)	11 (26%)	10 (22%)
Thrombosis	1 (3%)	2 (5%)	
Uterus	(44)	(45)	(49)
Angiectasis			1 (2%)
Hyperplasia, histiocytic, focal			1 (2%)
Metaplasia, squamous		1 (2%)	
Thrombosis	1 (2%)		
Endometrium, hyperplasia, cystic	34 (77%)	30 (67%)	35 (71%)
Mucosa, inflammation, suppurative	3 (7%)	7 (16%)	4 (8%)
Serosa, inflammation, suppurative	1 (2%)	4 (9%)	2 (4%)

Table D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Talc (continued)

	0 mg/m³	6 mg/m³	18 mg/m³
Hematopoietic System			
Bone marrow	(41)	(43)	(45)
Hyperplasia	1 (2%)	4 (9%)	5 (11%)
Myelofibrosis	28 (68%)	23 (53%)	27 (60%)
Myeloid cell, hyperplasia	1 (2%)	6 (14%)	3 (7%)
Lymph node	(46)	(46)	(49)
Iliac, hyperplasia, lymphoid			1 (2%)
Iliac, inflammation	1 (2%)		1 (2%)
Pancreatic, hyperplasia, lymphoid	1 (2%)		1 (2%)
Pancreatic, infiltration cellular, mixed cell			1 (2%)
Pancreatic, follicular, necrosis			1 (2%)
Renal, hyperplasia, lymphoid		2 (4%)	2 (4%)
Renal, infiltration cellular, mixed cell			1 (2%)
Renal, inflammation	1 (2%)	1 (2%)	1 (2%)
Renal, follicular, necrosis		2 (4%)	1 (2%)
Lymph node, bronchial	(38)	(37)	(43)
Hyperplasia, histiocytic		25 (68%)	39 (91%)
Hyperplasia, lymphoid		16 (43%)	20 (47%)
Infiltration cellular, mixed cell	1 (3%)		
Inflammation, acute	1 (3%)	1 (3%)	1 (2%)
Lymph node, mandibular	(35)	(38)	(36)
Cyst			1 (3%)
Depletion lymphoid	1 (3%)		
Hyperplasia, histiocytic	1 (3%)		
Hyperplasia, lymphoid		1 (3%)	3 (8%)
Hyperplasia, plasma cell	1 (3%)		
Infiltration cellular, mixed cell		1 (3%)	
Inflammation		1 (3%)	1 (3%)
Follicular, necrosis		1 (3%)	
Lymph node, mediastinal	(13)	(17)	(14)
Hyperplasia, histiocytic	1 (8%)	3 (18%)	2 (14%)
Hyperplasia, lymphoid		1 (6%)	2 (14%)
Infiltration cellular, mixed cell	1 (8%)		
Lymph node, mesenteric	(35)	(31)	(37)
Depletion lymphoid		1 (3%)	2 (5%)
Hematocyst			1 (3%)
Hyperplasia, histiocytic		1 (3%)	1 (3%)
Hyperplasia, lymphoid		2 (6%)	2 (5%)
Hyperplasia, plasma cell			1 (3%)
Infiltration cellular, mixed cell	5 (14%)	5 (16%)	5 (14%)
Inflammation		2 (6%)	1 (3%)
Follicular, necrosis	3 (9%)	12 (39%)	7 (19%)
Spleen	(45)	(44)	(50)
Congestion	2 (4%)		
Hematopoietic cell proliferation	8 (18%)	12 (27%)	10 (20%)
Hyperplasia, lymphoid	5 (11%)	8 (18%)	6 (12%)
Inflammation, suppurative	2 (4%)		1 (2%)
Capsule, inflammation, suppurative	2 (4%)	3 (7%)	3 (6%)
Lymphoid follicle, depletion lymphoid	2 (4%)	3 (7%)	5 (10%)
Lymphoid follicle, necrosis	2 (4%)	4 (9%)	2 (4%)
Thymus	(40)	(40)	(41)
Cyst	2 (5%)	2 (5%)	
Hyperplasia, plasma cell		1 (3%)	
Inflammation, suppurative		1 (3%)	1 (2%)
Necrosis	3 (8%)	5 (13%)	
Cortex, depletion lymphoid	8 (20%)	12 (30%)	15 (37%)

Table D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Talc (continued)

	0 mg/m³	6 mg/m³	18 mg/m³
Integumentary System			
Mammary gland	(41)	(45)	(48)
Abscess			1 (2%)
Edema	1 (2%)		
Skin	(46)	(46)	(50)
Alopecia	2 (4%)	2 (4%)	
Musculoskeletal System			
Bone	(46)	(48)	(50)
Periosteum, femur, proliferation connective tissue	1 (2%)		
Nervous System			
Brain	(46)	(48)	(50)
Hydrocephalus		2 (4%)	
Mineralization, focal	36 (78%)	33 (69%)	29 (58%)
Respiratory System			
Larynx	(42)	(43)	(48)
Inflammation, acute	1 (2%)		
Lung	(46)	(48)	(50)
Congestion	1 (2%)	3 (6%)	
Hyperplasia, histiocytic			1 (2%)
Hyperplasia, macrophage	2 (4%)	45 (94%)	43 (86%)
Inflammation, chronic active		25 (52%)	38 (76%)
Metaplasia, osseous, focal	1 (2%)		
Alveolar epithelium, hyperplasia, focal			1 (2%)
Perivascular, inflammation, suppurative		3 (6%)	1 (2%)
Pleura, inflammation, suppurative	1 (2%)	2 (4%)	5 (10%)
Nose	(46)	(46)	(50)
Cytoplasmic alteration, focal	29 (63%)	37 (80%)	40 (80%)
Developmental malformation	1 (2%)		
Erosion, focal	3 (7%)		1 (2%)
Inflammation, acute	6 (13%)	4 (9%)	5 (10%)
Ulcer, focal	1 (2%)		
Special Senses System			
Eye		(1)	
Inflammation, suppurative		1 (100%)	
Harderian gland	(2)	(2)	(1)
Inflammation, suppurative		1 (50%)	
Urinary System			
Kidney	(46)	(46)	(50)
Casts protein		2 (4%)	
Infarct	1 (2%)	1 (2%)	
Inflammation, focal	1 (2%)	1 (2%)	1 (2%)
Metaplasia, osseous, focal	1 (2%)		2 (4%)
Nephropathy, chronic	1 (2%)	1 (2%)	
Capsule, inflammation, suppurative	3 (7%)	6 (13%)	5 (10%)
Renal tubule, hyperplasia, focal		1 (2%)	

Table D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Talc (continued)

	0 mg/m^3	6 mg/m^3	18 mg/m^3
Urinary System (continued)			
Urinary bladder	(44)	(40)	(41)
Serosa, inflammation, suppurative		3 (8%)	3 (7%)
Submucosa, hyperplasia, lymphoid	1 (2%)		
Submucosa, inflammation, suppurative			1 (2%)

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.

APPENDIX E
ORGAN WEIGHTS
AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

TABLE E1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 6-Month Interim Evaluation in the Lifetime Inhalation Study of Talc[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
n	3	3	3
Necropsy body wt	379 ± 2	365 ± 9	351 ± 4*
Brain			
Absolute	2.061 ± 0.073	1.962 ± 0.035	1.964 ± 0.041
Relative	5.44 ± 0.22	5.38 ± 0.22	5.59 ± 0.10
Heart			
Absolute	1.087 ± 0.024	0.984 ± 0.047	1.008 ± 0.018
Relative	2.87 ± 0.07	2.69 ± 0.07	2.87 ± 0.03
R. Kidney			
Absolute	1.203 ± 0.055	1.155 ± 0.028	1.143 ± 0.025
Relative	3.17 ± 0.16	3.16 ± 0.01	3.25 ± 0.04
Liver			
Absolute	12.969 ± 0.336	11.658 ± 0.483	11.644 ± 0.613
Relative	34.20 ± 0.79	31.89 ± 0.65	33.11 ± 1.43
Lungs			
Absolute	1.196 ± 0.049	1.201 ± 0.060	1.600 ± 0.073**
Relative	3.15 ± 0.11	3.29 ± 0.19	4.55 ± 0.19**
Female			
n	3	3	3
Necropsy body wt	216 ± 10	210 ± 5	212 ± 7
Brain			
Absolute	1.801 ± 0.020	1.800 ± 0.030	1.860 ± 0.031
Relative	8.39 ± 0.33	8.57 ± 0.28	8.82 ± 0.39
Heart			
Absolute	0.679 ± 0.023	0.691 ± 0.031	0.716 ± 0.055
Relative	3.16 ± 0.11	3.29 ± 0.13	3.38 ± 0.20
R. Kidney			
Absolute	0.700 ± 0.043	0.775 ± 0.025	0.751 ± 0.030
Relative	3.25 ± 0.17	3.69 ± 0.10	3.55 ± 0.07
Liver			
Absolute	7.579 ± 0.502	7.253 ± 0.172	6.875 ± 0.409
Relative	35.13 ± 1.09	34.51 ± 0.33	32.47 ± 1.21
Lungs			
Absolute	1.006 ± 0.112	0.986 ± 0.064	1.090 ± 0.010
Relative	4.71 ± 0.65	4.69 ± 0.29	5.17 ± 0.21

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)

TABLE E2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 11-Month Interim Evaluation in the Lifetime Inhalation Study of Talc[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
n	2	3	3
Necropsy body wt	425 ± 10	406 ± 15	395 ± 14
Brain			
Absolute	2.018 ± 0.010	1.616 ± 0.306	2.020 ± 0.012
Relative	4.75 ± 0.13	3.97 ± 0.74	5.13 ± 0.16
Heart			
Absolute	1.161 ± 0.080	1.051 ± 0.063	1.079 ± 0.048
Relative	2.73 ± 0.12	2.58 ± 0.06	2.73 ± 0.09
R. Kidney			
Absolute	1.313 ± 0.008	1.242 ± 0.062	1.216 ± 0.069
Relative	3.09 ± 0.09	3.07 ± 0.26	3.07 ± 0.07
Liver			
Absolute	12.824 ± 0.065	12.454 ± 0.424	12.223 ± 0.618
Relative	30.20 ± 0.86	30.72 ± 1.47	30.92 ± 0.50
Lungs			
Absolute	1.228 ± 0.143	1.152 ± 0.043	1.979 ± 0.077**
Relative	2.90 ± 0.40	2.85 ± 0.18	5.02 ± 0.16**
Female			
n	3	3	3
Necropsy body wt	254 ± 7	249 ± 5	247 ± 10
Brain			
Absolute	1.863 ± 0.003	1.867 ± 0.036	1.845 ± 0.030
Relative	7.36 ± 0.22	7.52 ± 0.18	7.50 ± 0.19
Heart			
Absolute	0.858 ± 0.032	0.796 ± 0.020	0.753 ± 0.063
Relative	3.38 ± 0.06	3.20 ± 0.06	3.05 ± 0.19
R. Kidney			
Absolute	0.830 ± 0.007	0.839 ± 0.002	0.735 ± 0.034*
Relative	3.28 ± 0.11	3.38 ± 0.07	2.99 ± 0.13
Liver			
Absolute	7.878 ± 0.275	7.774 ± 0.130	7.537 ± 0.354
Relative	31.13 ± 1.53	31.30 ± 0.47	30.57 ± 0.50
Lungs			
Absolute	0.959 ± 0.037	1.039 ± 0.034	1.551 ± 0.163**
Relative	3.79 ± 0.20	4.18 ± 0.09	6.27 ± 0.48**

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)

Table E3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 18-Month Interim Evaluation in the Lifetime Inhalation Study of Talc[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
n	3	3	2
Necropsy body wt	446 ± 14	428 ± 10	430 ± 2
Brain			
Absolute	2.019 ± 0.043	1.965 ± 0.035	2.092 ± 0.004
Relative	4.53 ± 0.10	4.60 ± 0.17	4.86 ± 0.01
Heart			
Absolute	1.077 ± 0.065	1.027 ± 0.030	1.131 ± 0.103
Relative	2.41 ± 0.09	2.40 ± 0.07	2.63 ± 0.23
R. Kidney			
Absolute	1.913 ± 0.599	1.328 ± 0.063	1.317 ± 0.023
Relative	4.27 ± 1.31	3.10 ± 0.12	3.06 ± 0.06
Liver			
Absolute	14.329 ± 1.434	13.866 ± 0.882	12.520 ± 0.189
Relative	32.10 ± 3.01	32.38 ± 1.68	29.10 ± 0.56
Lungs			
Absolute	1.691 ± 0.100	1.852 ± 0.058	3.169 ± 0.121**
Relative	3.78 ± 0.13	4.34 ± 0.21	7.36 ± 0.25**
Female			
n	3	3	3
Necropsy body wt	305 ± 5	275 ± 4**	280 ± 4*
Brain			
Absolute	1.840 ± 0.028	1.827 ± 0.045	1.847 ± 0.013
Relative	6.04 ± 0.17	6.63 ± 0.11*	6.61 ± 0.13*
Heart			
Absolute	0.772 ± 0.015	0.706 ± 0.010*	0.765 ± 0.011
Relative	2.53 ± 0.08	2.56 ± 0.03	2.74 ± 0.01*
R. Kidney			
Absolute	0.929 ± 0.023	0.902 ± 0.038	0.955 ± 0.047
Relative	3.05 ± 0.12	3.28 ± 0.17	3.41 ± 0.13
Liver			
Absolute	8.750 ± 0.223	8.540 ± 0.648	8.904 ± 0.596
Relative	28.71 ± 0.35	31.03 ± 2.47	31.84 ± 1.94
Lungs			
Absolute	1.130 ± 0.026	1.395 ± 0.046**	2.600 ± 0.030**
Relative	3.71 ± 0.12	5.07 ± 0.11**	9.31 ± 0.18**

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)

TABLE E4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 24-Month Interim Evaluation in the Lifetime Inhalation Study of Talc[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
n	3	6	2
Necropsy body wt	406 ± 29	422 ± 12	392 ± 30
Brain			
Absolute	2.068 ± 0.015	2.023 ± 0.025	1.989 ± 0.008
Relative	5.15 ± 0.42	4.81 ± 0.11	5.10 ± 0.37
Heart			
Absolute	1.065 ± 0.022	1.126 ± 0.044	0.993 ± 0.026
Relative	2.66 ± 0.25	2.69 ± 0.18	2.54 ± 0.13
R. Kidney			
Absolute	1.720 ± 0.138	1.577 ± 0.048	1.649 ± 0.068
Relative	4.25 ± 0.32	3.76 ± 0.19	4.24 ± 0.50
Liver			
Absolute	15.298 ± 0.187	14.924 ± 0.480	14.344 ± 1.253
Relative	38.11 ± 3.23	35.55 ± 1.80	37.05 ± 6.03
Lungs			
Absolute	1.766 ± 0.177	2.150 ± 0.230	2.473 ± 0.674
Relative	4.40 ± 0.55	5.18 ± 0.69	6.48 ± 2.21
Female			
n	5	9	3
Necropsy body wt	296 ± 17	296 ± 10	262 ± 25
Brain			
Absolute	1.821 ± 0.023	1.826 ± 0.011	1.865 ± 0.012
Relative	6.24 ± 0.42	6.24 ± 0.21	7.23 ± 0.63
Heart			
Absolute	0.826 ± 0.014	0.826 ± 0.032	0.824 ± 0.045
Relative	2.83 ± 0.19	2.81 ± 0.10	3.16 ± 0.13
R. Kidney			
Absolute	1.118 ± 0.055	1.137 ± 0.044	1.021 ± 0.022
Relative	3.82 ± 0.26	3.85 ± 0.10	3.97 ± 0.44
Liver			
Absolute	11.218 ± 0.527	12.127 ± 0.672	9.966 ± 0.246
Relative	38.38 ± 2.74	41.16 ± 2.12	38.84 ± 4.59
Lungs			
Absolute	1.014 ± 0.104	1.447 ± 0.219	3.261 ± 0.115**
Relative	3.40 ± 0.23	4.88 ± 0.67	12.73 ± 1.62**

** Significantly different ($P \leq 0.01$) from the control group by Williams' or Dunnett's test
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)

TABLE E5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the Termination of the Lifetime Inhalation Study of Talc[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
n	8	12	13
Necropsy body wt	379 ± 17	397 ± 6	326 ± 12**
Brain			
Absolute	2.030 ± 0.016	2.041 ± 0.015	2.014 ± 0.019
Relative	5.45 ± 0.28	5.16 ± 0.09	6.29 ± 0.25*
Heart			
Absolute	1.385 ± 0.104	1.288 ± 0.041	1.302 ± 0.064
Relative	3.68 ± 0.26	3.26 ± 0.13	4.05 ± 0.22
R. Kidney			
Absolute	1.899 ± 0.151	1.847 ± 0.125	1.737 ± 0.101
Relative	5.09 ± 0.49	4.69 ± 0.37	5.39 ± 0.35
Liver			
Absolute	15.501 ± 0.861	16.562 ± 0.540	14.055 ± 0.936
Relative	41.03 ± 1.67	41.92 ± 1.73	42.85 ± 1.76
Lungs			
Absolute	2.154 ± 0.124	2.509 ± 0.068	4.026 ± 0.196**
Relative	5.76 ± 0.38	6.34 ± 0.21	12.65 ± 0.85**
Female			
n	12	13	9
Necropsy body wt	260 ± 14	247 ± 14	231 ± 9
Brain			
Absolute	1.975 ± 0.122	1.860 ± 0.020	1.847 ± 0.028
Relative	8.03 ± 0.95	7.89 ± 0.51	8.06 ± 0.27
Heart			
Absolute	1.020 ± 0.039	1.006 ± 0.026	1.047 ± 0.027
Relative	4.03 ± 0.24	4.33 ± 0.39	4.58 ± 0.20
R. Kidney			
Absolute	1.313 ± 0.047	1.235 ± 0.049	1.281 ± 0.079
Relative	5.21 ± 0.34	5.22 ± 0.36	5.66 ± 0.55
Liver			
Absolute	12.005 ± 0.660	12.567 ± 0.903	12.313 ± 0.642
Relative	46.35 ± 1.68	51.25 ± 2.90	53.69 ± 3.72
Lungs			
Absolute	1.575 ± 0.109	2.673 ± 0.362**	4.050 ± 0.228**
Relative	6.11 ± 0.35	11.77 ± 2.10*	17.83 ± 1.43**

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)

TABLE E6
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 6-Month Interim Evaluation in the 2-Year Inhalation Study of Talc[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
n	4	4	4
Necropsy body wt	31.3 ± 0.9	31.1 ± 0.9	32.1 ± 0.6
Brain			
Absolute	0.431 ± 0.028	0.458 ± 0.006	0.469 ± 0.008
Relative	13.81 ± 0.90	14.74 ± 0.23	14.60 ± 0.38
Heart			
Absolute	0.159 ± 0.003	0.165 ± 0.008	0.157 ± 0.011
Relative	5.10 ± 0.07	5.31 ± 0.33	4.88 ± 0.25
R. Kidney			
Absolute	0.303 ± 0.022	0.297 ± 0.018	0.292 ± 0.011
Relative	9.66 ± 0.40	9.58 ± 0.70	9.10 ± 0.33
Liver			
Absolute	1.737 ± 0.079	1.792 ± 0.066	1.731 ± 0.060
Relative	55.51 ± 1.06	57.75 ± 2.77	53.84 ± 1.19
Lungs			
Absolute	0.165 ± 0.008	0.149 ± 0.010	0.173 ± 0.017
Relative	5.29 ± 0.35	4.78 ± 0.27	5.35 ± 0.44
Female			
n	4	4	4
Necropsy body wt	27.1 ± 0.9	27.2 ± 1.7	29.5 ± 1.4
Brain			
Absolute	0.474 ± 0.007	0.482 ± 0.008	0.474 ± 0.019
Relative	17.52 ± 0.36	17.85 ± 0.81	16.10 ± 0.67
Heart			
Absolute	0.142 ± 0.004	0.133 ± 0.005	0.145 ± 0.006
Relative	5.27 ± 0.30	4.92 ± 0.19	4.92 ± 0.15
R. Kidney			
Absolute	0.201 ± 0.011	0.203 ± 0.004	0.217 ± 0.008
Relative	7.40 ± 0.20	7.53 ± 0.34	7.37 ± 0.13
Liver			
Absolute	1.541 ± 0.099	1.640 ± 0.138	1.628 ± 0.033
Relative	56.86 ± 2.92	60.01 ± 1.74	55.38 ± 1.91
Lungs			
Absolute	0.190 ± 0.019	0.164 ± 0.011	0.178 ± 0.011
Relative	7.11 ± 0.96	6.03 ± 0.28	6.04 ± 0.26

[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)

TABLE E7
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 12-Month Interim Evaluation in the 2-Year Inhalation Study of Talc[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
n	4	4	4
Necropsy body wt	34.6 ± 1.7	37.2 ± 0.3	33.1 ± 1.3
Brain			
Absolute	0.478 ± 0.020	0.475 ± 0.009	0.475 ± 0.009
Relative	13.87 ± 0.31	12.76 ± 0.16	14.39 ± 0.38
Heart			
Absolute	0.196 ± 0.023	0.195 ± 0.005	0.205 ± 0.023
Relative	5.62 ± 0.37	5.23 ± 0.10	6.21 ± 0.69
R. Kidney			
Absolute	0.334 ± 0.007	0.339 ± 0.020	0.311 ± 0.027
Relative	9.71 ± 0.28	9.12 ± 0.52	9.41 ± 0.86
Liver			
Absolute	1.612 ± 0.052	1.886 ± 0.124	1.928 ± 0.240
Relative	46.77 ± 0.79	50.72 ± 3.25	58.55 ± 8.01
Lungs			
Absolute	0.157 ± 0.009	0.216 ± 0.018	0.243 ± 0.032*
Relative	4.54 ± 0.17	5.80 ± 0.46	7.30 ± 0.72**
Female			
n	3	4	4
Necropsy body wt	32.1 ± 2.4	33.3 ± 1.3	28.7 ± 1.2
Brain			
Absolute	0.478 ± 0.006	0.488 ± 0.005	0.491 ± 0.008
Relative	15.04 ± 1.16	14.74 ± 0.70	17.16 ± 0.55
Heart			
Absolute	0.151 ± 0.004	0.162 ± 0.008	0.190 ± 0.010*
Relative	4.72 ± 0.23	4.91 ± 0.42	6.64 ± 0.47*
R. Kidney			
Absolute	0.225 ± 0.010	0.231 ± 0.008	0.230 ± 0.011
Relative	7.03 ± 0.22	6.97 ± 0.40	8.01 ± 0.10
Liver			
Absolute	1.470 ± 0.105	1.796 ± 0.036*	1.477 ± 0.093
Relative	46.04 ± 3.71	54.20 ± 2.55	51.40 ± 2.48
Lungs			
Absolute	0.151 ± 0.019	0.191 ± 0.014	0.207 ± 0.015*
Relative	4.68 ± 0.23	5.78 ± 0.61	7.19 ± 0.24**

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)

TABLE E8
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 18-Month Interim Evaluation in the 2-Year Inhalation Study of Talc[a]

	0 mg/m^3	6 mg/m^3	18 mg/m^3
Male			
n	4	4	4
Necropsy body wt	33.1 ± 3.0	37.5 ± 2.1	35.4 ± 1.7
Brain			
Absolute	0.467 ± 0.007	0.470 ± 0.009	0.496 ± 0.014
Relative	14.51 ± 1.44	12.63 ± 0.58	14.10 ± 0.76
Heart			
Absolute	0.193 ± 0.017	0.186 ± 0.011	0.203 ± 0.006
Relative	6.18 ± 1.29	5.00 ± 0.35	5.77 ± 0.22
R. Kidney			
Absolute	0.342 ± 0.007	0.361 ± 0.021	0.350 ± 0.009
Relative	10.66 ± 1.23	9.66 ± 0.47	9.91 ± 0.22
Liver			
Absolute	1.844 ± 0.228	1.796 ± 0.080	1.748 ± 0.113
Relative	57.08 ± 7.95	48.07 ± 1.26	49.28 ± 1.45
Lungs			
Absolute	0.229 ± 0.034	0.238 ± 0.013	0.345 ± 0.032*
Relative	7.45 ± 2.01	6.42 ± 0.57	9.79 ± 0.91
Female			
n	4	4	4
Necropsy body wt	32.1 ± 1.2	31.9 ± 1.6	27.6 ± 1.0*
Brain			
Absolute	0.483 ± 0.007	0.467 ± 0.019	0.501 ± 0.038
Relative	15.10 ± 0.59	14.73 ± 0.90	18.33 ± 1.91
Heart			
Absolute	0.155 ± 0.008	0.154 ± 0.011	0.164 ± 0.010
Relative	4.85 ± 0.28	4.87 ± 0.47	5.96 ± 0.48
R. Kidney			
Absolute	0.238 ± 0.009	0.233 ± 0.011	0.228 ± 0.007
Relative	7.41 ± 0.28	7.35 ± 0.45	8.32 ± 0.55
Liver			
Absolute	1.446 ± 0.056	1.592 ± 0.034	1.318 ± 0.055[b]
Relative	45.10 ± 1.35	50.17 ± 2.02	48.69 ± 0.30[b]
Lungs			
Absolute	0.223 ± 0.008	0.242 ± 0.018	0.299 ± 0.018**
Relative	6.96 ± 0.07	7.65 ± 0.73	10.90 ± 0.87**

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)
[b] n=3

TABLE E9
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the Termination of 2-Year Inhalation Study of Talc[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
n	30	28	32
Necropsy body wt	33.4 ± 0.5	32.1 ± 0.8	31.2 ± 0.4**
Brain			
Absolute	0.461 ± 0.004	0.458 ± 0.004	0.460 ± 0.005
Relative	13.90 ± 0.22	14.50 ± 0.34	14.78 ± 0.19*
Heart			
Absolute	0.183 ± 0.003	0.181 ± 0.004	0.183 ± 0.005
Relative	5.52 ± 0.12	5.68 ± 0.10	5.88 ± 0.15
R. Kidney			
Absolute	0.361 ± 0.010	0.362 ± 0.010	0.354 ± 0.006
Relative	10.85 ± 0.27	11.28 ± 0.16	11.34 ± 0.18
Liver			
Absolute	1.845 ± 0.064	1.733 ± 0.073[b]	1.535 ± 0.033**[c]
Relative	55.64 ± 2.21	53.14 ± 1.72[b]	49.27 ± 1.03*[c]
Lungs			
Absolute	0.252 ± 0.008[c]	0.258 ± 0.009[b]	0.408 ± 0.011**
Relative	7.47 ± 0.25[c]	8.01 ± 0.24[b]	13.08 ± 0.33**
Female			
n	30	23	25
Necropsy body wt	31.4 ± 0.6	31.7 ± 0.7	30.7 ± 0.5
Brain			
Absolute	0.484 ± 0.004	0.469 ± 0.006	0.477 ± 0.003
Relative	15.53 ± 0.26	14.93 ± 0.28	15.59 ± 0.20
Heart			
Absolute	0.164 ± 0.005	0.190 ± 0.009**	0.163 ± 0.003
Relative	5.24 ± 0.15	6.02 ± 0.28**	5.32 ± 0.09
R. Kidney			
Absolute	0.251 ± 0.007[d]	0.265 ± 0.010	0.257 ± 0.007[e]
Relative	8.03 ± 0.17[d]	8.38 ± 0.27	8.37 ± 0.14[e]
Liver			
Absolute	1.816 ± 0.089	1.770 ± 0.107[f]	1.761 ± 0.083[e]
Relative	57.41 ± 2.25	55.45 ± 3.13[f]	56.94 ± 1.93[e]
Lungs			
Absolute	0.276 ± 0.014	0.293 ± 0.012	0.410 ± 0.010**
Relative	8.80 ± 0.42	9.28 ± 0.34	13.39 ± 0.28**

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)
[b] n=27
[c] n=28
[d] n=29
[e] n=24
[f] n=22

APPENDIX F
LUNG BURDEN, PULMONARY FUNCTION, AND LUNG BIOCHEMISTRY IN RATS

METHODS

Lung Burden

Lung talc burden was measured to determine the relationship between the exposure concentration and the amount of talc deposited and retained within the pulmonary region of the respiratory tract. The method used for analyzing for talc in lungs has been published (Hanson *et al.*, 1985). Lung burdens were determined on 3 male and 3 female rats from each exposure group sacrificed at 27, 47, 79, and 105 weeks after the start of exposure. The analysis was based on determination of acid insoluble magnesium in the lung. MRI reported that the value for the magnesium was 19.33% for batch 02 and 19.47% for batch 03. These values and the results of the analysis at LITRI were close to the theoretical value of magnesium for talc (19.22%). Since rats sacrificed at 27, 47, and 79 weeks had been exposed to only batch 02 of talc, 19.33% magnesium was used to calculate the quantity of talc for these rats. Because batch 03 was used for the last 4 months of exposure and lung burdens of rats after 105 weeks of exposure to talc would be expected to contain substantial amounts of batch 03 talc, 19.47% magnesium was used to calculate the quantity of talc deposited in the lungs of these rats.

All operations in conjunction with tissue analysis for talc were done while wearing talc-free gloves. Left lung lobes were weighed at necropsy and stored frozen (-20° C) until used. Lungs were homogenized using water and the proteins were precipitated with 70% perchloric acid. The individual samples were filtered and washed with 5% trichloroacetic acid (TCA) to remove perchlorates. Washing continued until magnesium levels in the wash were within 10% of levels in the TCA solution ($\leq$ 0.03 ppm magnesium). Filters and tissue residues were placed in 15 mL porcelain crucibles, dried slowly (200° C), and then ashed at 600° C for 1 hour. Ashed samples were transferred to Teflon beakers using 2 mL HCl and evaporated to dryness. Samples were then digested in hydrofluoric acid (HF), and the HF evaporated. Additional HF was added and reevaporated. Sulfuric acid was added to remove trace HF, and samples were then diluted with distilled water and analyzed for magnesium by atomic absorbance (Perkin Elmer, Model 306, Atomic Absorption Spectrophotometer) with a magnesium hollow cathode lamp and an air acetylene flame (Hanson *et al.*, 1985).

Pulmonary Function

Ten male and 10 female rats from each exposure level were assigned for respiratory function analyses. Respiratory function was measured at 6 months (27 weeks), 10 months (43 weeks), and 18 months (79 weeks). At 24 months (103 to 104 weeks) of exposure, respiratory function was performed on all surviving rats not assigned to the lifetime study. Respiratory function was measured by noninvasive techniques, using methods previously published (Harkema *et al.*, 1982).

Tests were conducted using a 1.4 L combination flow and pressure plethysmograph. Flows were measured by measuring differential pressures across a wire screen pneumotachograph in the plethysmograph wall. Volumes were obtained by integration (Model 6, Pulmonary Mechanics Analyzer, Buxco Electronics, Sharon, CT). In the pressure mode, used only for measuring functional residual capacity, the pneumotachograph hole was sealed and volume changes were measured as pressure changes. The plethysmograph was maintained at approximately 37° C by a resistance element. Transpulmonary pressure was measured using transducers connected to the external airway and a liquid-filled, 2.2 mm O.D. esophageal catheter.

A positive-negative pressure respirator system was used to induce quasistatic and forced respiratory movements, simulating the movements performed voluntarily by man. Reservoirs maintained at +40 and -50 cm H_2O were connected to the airway by solenoid valves. Inspiratory and quasistatic expiratory flow rates were limited by calibrated needle valves to 5 and 3 mL/sec, respectively. Inspirations were stopped automatically at a transpulmonary pressure of 30 cm H_2O, defining the lung volume at that distending pressure as total lung capacity (TLC). Forced inhalations were induced from TLC by opening the airway to the negative pressure reservoir via a rapidly opening valve having a 9.5 mm I.D., with no intentional flow restriction between the valve and the reservoir.

The rats were anesthetized with halothane and intubated orally with a tracheal catheter 5.5 cm long × 1.8 mm I.D., fabricated from a 14-gauge intravenous catheter as previously described (Mauderly, 1977).

The breathing port in the plethysmograph wall was a luer fitting drilled to 2.5 mm I.D. The frequency response of the plethysmograph-respirator-tracheal catheter system has been tested and found adequate for forced expiratory events in rats. No phase lag among flow, pressure and volume signals has been found in the frequency range of spontaneous breathing.

Rats were anesthetized, intubated and placed prone in the plethysmograph. The esophageal catheter was adjusted to maximize the recorded transpulmonary pressure signal. Anesthetic depth was adjusted to yield a respiratory frequency of 50 to 60 per minute. Respiratory frequency, tidal volume, minute volume, dynamic lung compliance, and total pulmonary resistance were recorded during spontaneous respiration, time-averaged by a data logger and displayed on a teletype terminal.

Prior to each subsequent measurement procedure, the rat's lung was manually inflated with a syringe to induce apnea. A quasistatic deflation from TLC to residual volume allowed measurement of vital capacity and the quasistatic expiratory pressure-volume curve. Quasistatic lung chord compliance was measured as the slope of the curve over the chord between the apneic lung volume and the volume at +10 cm H_2O pressure. Maximum quasistatic compliance was measured as the steepest slope of the pressure-volume curve over any 2 cm H_2O pressure interval. Functional residual capacity was measured by the barometric method (Dubois *et al.*, 1956) from recordings of lung volume and airway pressure changes as the rat resumed breathing against a blocked airway. From these measurements, all subdivisions of lung volume were calculated including residual volume.

Alveolar-capillary gas exchange was evaluated by a single-breath, CO diffusing capacity test (Ogilvie *et al.*, 1957). The lungs were inflated with a gas mixture containing CO and Ne in air to 20 cm H_2O transpulmonary pressure. After 6 seconds, one-half of the gas was withdrawn and the remaining gas collected for analysis by gas chromatography. The lung volume when inflated with the mixture was measured by neon dilution.

A forced inhalation was performed as described above, and the maneuver analyzed by a microprocessor in the data logger (Model D-12, Buxco). Data included forced vital capacity (FVC), the percentage of FVC exhaled in 0.1 second, flow rates at peak flow, and at 50%, 25%, and 10% of FVC.

A single-breath nitrogen washout was performed by recording volume and nitrogen concentration of expirate during a slow deflation after an inflation to TLC with oxygen. The slope of phase III ("alveolar plateau") of the washout curve was calculated to assess the uniformity of intrapulmonary gas distribution.

Lung Biochemistry

All surviving rats from each exposure group (the 3 males and 3 females originally assigned for lung burden/histology and the 10 males and 10 females from physiology/biochemistry) were sacrificed after 105 weeks of exposure.

The rats were anesthetized with halothane and sacrificed by exsanguination from the abdominal aorta or renal artery. The heart and lung block was removed, the right apical, right cardiac, and right intermediate portions of each rat lung were given endobronchial saline lavage (6 mL total volume in three, 2.0 mL washes of saline), and the bronchoalveolar lavage (BAL) fluid was centrifuged at 300 × G to separate the cells from the supernatant fluid.

Airway Fluid Enzymes and Cytology Measurements

In this study, BAL fluid was analyzed to determine the degree of:

1) Cell injury as indicated by concentration of lactate dehydrogenase (LDHP)
2) Chronic inflammatory response as indicated by presence of increased numbers of polymorphonuclear leukocytes (PMN) and pulmonary alveolar macrophages (AM) as well as increased protein and alkaline phosphatase activity

3) Lysosomal activation as indicated by ß-glucuronidase and acid proteinase activity. Elevated enzyme activities have been observed in BAL fluid from rodents exposed to particles. These enzymes may be associated with the breakdown of necrotic tissues.
4) Response to oxidant injury as indicated by increased glutathione reductase activity.

The supernatant fluid was analyzed by spectrophotometric, kinetic, and enzymatic analyses for the activities of ß-glucuronidase, LDHP, glucose-6-phosphate dehydrogenase, alkaline phosphatase, glutathione reductase, and glutathione peroxidase. Acid proteinase was measured by the release of radiolabeled globin peptides from the trichloroacetic acid-precipitable protein substrate, and total protein was analyzed colorimetrically (Henderson *et al.*, 1985).

Numbers of total nucleated cells recovered in lavage fluid were determined using a cell counter (Coulter Electronic, Hileah, FL) or a hemocytometer. Cytocentrifuge preparations of resuspended cells were made, stained with Wright's stain (Diff-Quick, Curtin Matheson Scientific, Denver, CO) and the differential cell count determined.

Alveolar macrophages (AM) were recovered from BAL fluid of the same rats as described above. The cells (1×10^6) were suspended in Roswell Park Memorial Institute (RPMI) 1640 culture medium and pelleted by centrifugation and the supernatant RPMI removed. Cells were resuspended in 1 mL of a 1% suspension of IgG antibody-sensitized sheep red blood cells (SRBC) in RPMI 1640. The antibody-sensitized SRBC were made as previously described (Harmsen and Jeska, 1980). The subagglutinating titer of heat-inactivated rabbit anti-SRBC serum was used to sensitize the SRBC. The AM and SRBC suspensions were incubated at 37° C for 1 hour in a humidified atmosphere of 5% CO_2 in air. The AM and SRBC were sedimented by centrifugation and the supernatant discarded. Unphagocytized SRBC were removed by lysing the RBC with water for 30 seconds. Lysing of unphagocytized SRBC was stopped by the addition of an equal volume of saline and cytocentrifuge preparations were made. The slides were stained with Wright's stain (Diff-Quik, American Scientific Products, McGaw Park, IL) and the percent of AM phagocytizing SRBC was determined by light microscopy. Three fields of 100 cells per preparation were counted. Viability was determined by trypan blue exclusion.

Lung Tissue Collagen and Proteinase

In this study, rats sacrificed at 105 weeks of talc exposure were used for collagen metabolism, protein synthesis, and proteinase activity measurements. Tissue and BAL fluid from single rats were used for analyses.

To estimate collagen and protein synthesis, ^{14}C-proline (0.1 μCi/g body weight) was injected intraperitoneally approximately 2 to 3 hours prior to sacrifice. Lung lobes to be analyzed for collagen were frozen in liquid nitrogen and pulverized. The pulverized lungs were extracted overnight in 0.5M acetic acid at 4° C, and centrifuged to separate the insoluble material from the supernatant fluid. The supernatant fluid was separated into high and low molecular weight fractions using Amicon Cones with a size cutoff of approximately 50 kDa.

All samples for collagen analyses from lung and lavage supernatant fluid were hydrolyzed for approximately 18 hours in 6N HCl at 110° C to convert proteins to their individual amino acids, were evaporated to dryness to remove the HCl, and were resuspended in 0.001 N HCl prior to analysis.

Collagen quantity was measured and multiplied by 7.46 to convert BAL or lung tissue hydroxyproline content to BAL or lung tissue collagen content, taking into account that collagen is approximately 13% hydroxyproline by weight (Neuman and Logan, 1950).

Radioactive proline and hydroxyproline were quantitated in the low molecular weight supernatant fluid fraction and in a sample containing both the high molecular weight supernatant fluid fraction and the acetic acid insoluble fraction. Following this, the radioactive proline and hydroxyproline quantities were

used to calculate the noncollagenous protein synthesis, the collagen production, and the intracellular collagen degradation.

Noncollagenous protein synthesis was measured as the total radioactive proline incorporation into lung tissue minus the incorporation into lung tissue which was related to collagen synthesis. The radioactive proline in collagen was assumed to be equal to the radioactive hydroxyproline, thus, incorporation into collagen was calculated as twice the radioactive hydroxyproline. Collagen production (% of newly synthesized protein that was collagen) was calculated as the percentage of the total incorporation of proline into all proteins constituted by collagen, and adjusted for the 5.4-fold difference in the content of total amino acids (proline and hydroxyproline) between collagen and noncollagenous protein (Pickrell *et al.*, 1987). Intracellular collagen degradation (as a percent of newly synthesized collagen) was calculated as the percentage of total radioactive hydroxyproline in collagen constituted by low molecular weight radioactive hydroxyproline-containing peptides.

Lung tissue proteinase activity was measured as the release of ^{14}C-leucine from prelabeled globin at pH 4.2 and 7.5 (Gregory and Pickrell, 1982; Harkema *et al.*, 1984; Pickrell *et al.*, 1987). Acid proteinase activity was inhibited by leupeptin to indicate either neutrophil and macrophage cathepsin B (inhibited) or macrophage cathepsin D (not inhibited)-like activity. Neutral proteinase activity was inhibited by 1,10-phenanthroline to indicate either macrophage elastase (inhibited) or neutrophil elastase-cathepsin G (not inhibited)-like activity.

Table F1
Number of Rats Evaluated for Lung Talc Burden, Pulmonary Function, and Lung Biochemistry

	Male			Female		
	0 mg/m³	6 mg/m³	18 mg/m³	0 mg/m³	6 mg/m³	18 mg/m³
Lung Burden						
6-Month Interim	–[a]	3	3	–	3	3
11-Month Interim	–	3	3	–	3	3
18-Month Interim	–	3	3	–	2	3
24-Month Interim	–	6	9	–	2	3
Pulmonary Function						
6-Month Interim	9	10	10	10	10	10
11-Month Interim	9	10	10	10	10	10
18-Month Interim	9	10	10	9	9	9
24-Month Interim	3	6	3	6	9	3
Lung Biochemistry						
24-Month Interim	3	6	2	5	9	3

[a] Lung burden not measured in 0 mg/m³ rats.

TABLE F2
Lung Talc Burden (Normalized to Control Lung Weight) of Rats[a]

	6 months	12 months	18 months	24 months
Male				
0 mg/m³	–[b]	–	–	–
6 mg/m³	2.63 ± 0.24	4.38 ± 0.59	7.31 ± 0.71	10.45 ± 1.26
18 mg/m³	10.83 ± 0.23	20.96 ± 2.04	27.57 ± 0.91	24.15 ± 3.41
Female				
0 mg/m³	–	–	–	–
6 mg/m³	2.43 ± 0.19	4.71 ± 0.26	7.66 ± 0.34	9.10 ± 0.88
18 mg/m³	8.34 ± 0.12	14.16 ± 3.36	24.33 ± 0.63	29.40 ± 2.40

[a] Units are presented as mg talc/g control lung.
[b] No measurements taken

TABLE F3
Lung Talc Burden (Normalized to Exposure Concentration) of Rats[a]

	Male		Female	
	6 mg/m³	18 mg/m³	6 mg/m³	18 mg/m³
6-Month Interim	0.439 ± 0.040	0.602 ± 0.013*	0.406 ± 0.032	0.464 ± 0.007*
12-Month Interim	0.731 ± 0.098	1.165 ± 0.113*	0.785 ± 0.043	0.787 ± 0.187
18-Month Interim	1.22 ± 0.12	1.53 ± 0.05	1.28 ± 0.06	1.35 ± 0.04
24-Month Interim	1.74 ± 0.21	1.34 ± 0.19	1.52 ± 0.15	1.63 ± 0.13

* Significantly different ($P \leq 0.05$) from the 6 mg/m³ group by Dunn's or Shirley's test
[a] Units are presented as mg talc/g control lung/mg/m³

TABLE F4
Bronchoalveolar Lavage Fluid Enzymes of Rats at the 24-Month Interim Evaluation

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
ß-Glucuronidase[a]	1.09 ± 0.40	18.86 ± 3.20*	89.24 ± 14.24**
Lactate dehydrogenase	1,634 ± 545	3,193 ± 606	8,262 ± 380*
Alkaline phosphatase	364.7 ± 147	572.8 ± 86.8	1,604.7 ± 143*
Glutathione reductase	103.03 ± 16.43	99.35 ± 19.79	110.99 ± 51.27
Total protein[b]	1.78 ± 0.40	3.12 ± 0.64	5.79 ± 0.55*
Female			
ß-Glucuronidase	3.33 ± 0.97	41.05 ± 4.39**	154.16 ± 17.21**
Lactate dehydrogenase	1,655 ± 266	3,906 ± 444*	14E3 ± 1E3**
Alkaline phosphatase	427.8 ± 30.9	853.6 ± 79.7**	2,504.7 ± 221**
Glutathione reductase	100.6 ± 1.7	135.2 ± 22.4	460.0 ± 44.8*
Total protein	1.20 ± 0.22	4.30 ± 0.36**	12.96 ± 0.28**

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
a Units presented as mIU/g control lung
b Units presented as mg/g control lung

TABLE F5
Bronchoalveolar Lavage Fluid Cell Populations of Rats at the 24-Month Interim Evaluation

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
Polymorphonuclear cells[a]	0.333 ± 0.167	24.417 ± 2.557*	32.500 ± 3.000*
Lymphocytes	0.000 ± 0.000	0.500 ± 0.258	0.500 ± 0.500
Macrophages	93.67 ± 3.72	70.25 ± 2.53*	62.75 ± 1.75*
Epithelial cells	6.00 ± 3.61	4.83 ± 1.41	4.25 ± 1.75
Female			
Polymophonuclear cells	0.625 ± 0.315	25.778 ± 2.673**	37.000 ± 1.528**
Lymphocytes	0.000 ± 0.000	0.722 ± 0.188*	1.333 ± 0.667*
Macrophages	91.38 ± 1.75	71.22 ± 2.95**	57.33 ± 4.67**
Epithelial cells	8.00 ± 2.01	2.28 ± 0.50*	4.33 ± 2.60

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
a Units presented as percent of total cells

TABLE F6
Viability and Phagocytic Activity of Macrophages in Bronchoalveolar Fluid of Rats at the 24-Month Interim Evaluation

	0 mg/m^3	6 mg/m^3	18 mg/m^3
Male			
Viability[a]	63.67 ± 5.91	66.73 ± 1.59	57.70 ± 5.00
Phagocytic activity[b]	83.13 ± 4.54	63.12 ± 8.14	65.30[c]
Female			
Viability	82.65 ± 9.65	74.64 ± 3.24	61.00 ± 4.42
Phagocytic activity	75.60 ± 5.14	66.51 ± 8.09	70.15 ± 2.85

[a] Units are presented as percent viable cells.
[b] Units are presented as percent cells phagocytizing sheep erythrocytes.
[c] n=1; no statistic calculated

TABLE F7
Lung Collagen Metabolism and Protein Synthesis in Rats at the 24-Month Interim Evaluation

	0 mg/m^3	6 mg/m^3	18 mg/m^3
Male			
Lavage fluid collagenous peptides[a]	39.79 ± 5.07	46.99 ± 6.51	79.21 ± 13.73
Total lung collagen[b]	13.87 ± 0.60	15.98 ± 0.39*	18.88 ± 3.35*
Collagen production[c]	1.58 ± 0.17	1.60 ± 0.17	1.63 ± 0.22
Collagen degradation[d]	31.67 ± 1.72	27.74 ± 1.42	9.18 ± 2.38*
Non-collagenous protein synthesis[e]	142.1 ± 14.5	199.8 ± 22.1*	312.2 ± 10.6**
Female			
Lavage fluid collagenous peptides	78.27 ± 11.64	115.36 ± 8.61*	174.71 ± 13.56**
Total lung collagen	14.32 ± 0.66	19.95 ± 1.58*	36.47 ± 3.39**
Collagen production	0.982 ± 0.185	1.804 ± 0.144*	2.264 ± 0.347**
Collagen degradation	14.41 ± 2.44	21.59 ± 4.99	9.38 ± 1.63
Non-collagenous protein synthesis	173.9 ± 34.5	325.8 ± 90.9	554.3 ± 107*

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Units are presented as μg/g control lung.
[b] Units are presented as mg/g control lung.
[c] Units are presented as percent new protein.
[d] Units are presented as percent new collagen.
[e] Units are presented as dpm x 10^3/g control lung.

Table F8
Proteinase Activity in Lavage Fluid and Lung Homogenate Supernatant Fluid of Rats at the 24-Month Interim Evaluation[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
Lavage Fluid			
Acid Proteinase	0.994 ± 0.329	1.866 ± 0.174	4.307 ± 0.218*
Cathepsin D	0.147 ± 0.147	0.599 ± 0.150	2.420 ± 0.147**
Cathepsin B	0.924 ± 0.415	1.267 ± 0.094	1.887 ± 0.365
Homogenate Supernatant Fluid			
Acid Proteinase	10.92 ± 0.64	17.51 ± 0.90*	25.13 ± 1.50**
Cathepsin D	8.53 ± 0.91	14.04 ± 0.62*	21.03 ± 1.56**
Cathepsin B	2.39 ± 0.41	3.48 ± 0.37	4.10 ± 0.06*
Neutral Proteinase	0.715 ± 0.168	2.417 ± 0.304*	4.505[b]
PMN Elastase Cathepsin G	0.490 ± 0.218	1.936 ± 0.242*	4.457 ± 0.377**
Macrophage Elastase Collagenase	0.225 ± 0.099	0.482 ± 0.077	0.000[b]
Female			
Lavage Fluid			
Acid Proteinase	1.52 ± 0.12	3.46 ± 0.33*	6.05 ± 0.73**
Cathepsin D	0.015 ± 0.015	1.310 ± 0.292*	4.043 ± 0.578**
Cathepsin B	1.61 ± 0.26	2.15 ± 0.22	2.01 ± 0.17
Homogenate Supernatant Fluid			
Acid Proteinase	14.04 ± 0.95	29.43 ± 1.18**	38.61 ± 1.81**
Cathepsin D	10.05 ± 0.68	22.97 ± 1.07**	30.25 ± 1.60**
Cathepsin B	3.99 ± 0.58	6.46 ± 0.60*	8.37 ± 0.42**
Neutral Proteinase	0.648 ± 0.087	5.040 ± 0.418**	12.293 ± 1.598**
PMN Elastase Cathepsin G	0.785 ± 0.142	4.351 ± 0.261**	10.313 ± 2.694**
Macrophage Elastase Collagenase	0.054 ± 0.037	0.683 ± 0.175*	2.012 ± 1.126*

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
a Units are presented as mg/hour/mg control lung.
b n=1; no statistic calculated

TABLE F9
Respiratory Frequency of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	57.11 ± 0.86	55.00 ± 1.13	54.00 ± 0.75*
11-Month Interim	55.33 ± 1.11	56.10 ± 0.92	53.50 ± 0.99
18-Month Interim	56.50 ± 1.34	55.40 ± 1.08	54.60 ± 1.13
24-Month Interim	57.67 ± 1.20	56.50 ± 1.80	56.67 ± 1.86
Female			
6-Month Interim	52.10 ± 0.55	54.50 ± 1.19	54.30 ± 0.90
11-Month Interim	53.60 ± 0.73	53.70 ± 1.10	55.20 ± 0.94
18-Month Interim	55.44 ± 1.12	54.56 ± 0.93	55.22 ± 1.41
24-Month Interim	57.67 ± 1.23	54.44 ± 0.93	59.00 ± 0.58

* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test
[a] Units are presented as b/min; ratio is (dosed group mean/control group mean)×100

TABLE F10
Total Lung Capacity of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	19.86 ± 0.54	19.48 ± 0.46	19.25 ± 0.39
11-Month Interim	20.06 ± 0.32	18.44 ± 0.39**	17.67 ± 0.45**
18-Month Interim	20.30 ± 0.45	18.87 ± 0.41*	16.34 ± 0.52**
24-Month Interim	20.50 ± 0.83	20.20 ± 0.28	16.47 ± 1.53
Female			
6-Month Interim	14.20 ± 0.25	14.56 ± 0.27	13.80 ± 0.27
11-Month Interim	13.29 ± 0.21	12.91 ± 0.17	12.06 ± 0.26**
18-Month Interim	13.94 ± 0.26	12.68 ± 0.28**	11.43 ± 0.31**
24-Month Interim	14.85 ± 0.31	13.73 ± 0.34*	11.50 ± 1.07**

* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test
** P=≤.01
[a] Units are presented as mL; ratio is (dosed group mean/control group mean)×100

TABLE F11
Total Lung Capacity/Kilogram Body Weight of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	51.63 ± 1.05	51.45 ± 1.03	53.32 ± 0.78
11-Month Interim	47.71 ± 0.99	44.11 ± 0.87*	43.42 ± 0.74**
18-Month Interim	45.92 ± 1.58	42.98 ± 1.15	38.74 ± 1.50**
24-Month Interim	51.05 ± 4.36	48.49 ± 1.40	44.16 ± 1.29
Female			
6-Month Interim	67.73 ± 1.26	67.06 ± 1.65	65.41 ± 1.50
11-Month Interim	55.21 ± 1.91	52.37 ± 1.05	50.24 ± 1.19
18-Month Interim	45.78 ± 1.26	43.40 ± 1.18	43.26 ± 2.42
24-Month Interim	49.03 ± 1.31	48.93 ± 2.49	44.54 ± 0.51

* Significantly different ($P \leq 0.05$) from the control by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Units are presented as mL/kg; ratio is (dosed group mean/control group mean)×100

TABLE F12
Tidal Volume of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	1.83 ± 0.09	1.90 ± 0.08	2.01 ± 0.10
11-Month Interim	1.94 ± 0.06	1.91 ± 0.06	1.93 ± 0.06
18-Month Interim	1.66 ± 0.08	1.63 ± 0.08	1.74 ± 0.08
24-Month Interim	1.50 ± 0.00	1.85 ± 0.16	2.13 ± 0.19*
Female			
6-Month Interim	1.65 ± 0.07	1.53 ± 0.11	1.40 ± 0.07*
11-Month Interim	1.66 ± 0.07	1.68 ± 0.06	1.43 ± 0.09
18-Month Interim	1.54 ± 0.04	1.34 ± 0.06*	1.40 ± 0.03*
24-Month Interim	1.43 ± 0.08	1.39 ± 0.09	1.37 ± 0.15

* Significantly different ($P \leq 0.05$) from the control by Dunn's or Shirley's test
[a] Units are presented as mL; ratio is (dosed group mean/control group mean)×100

TABLE F13
Minute Volume of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	102.5 ± 3.9	104.8 ± 4.2	104.8 ± 3.4
11-Month Interim	104.5 ± 3.4	106.2 ± 2.3	100.5 ± 2.8
18-Month Interim	97.34 ± 2.79	90.83 ± 3.45	95.87 ± 4.61
24-Month Interim	92.53 ± 2.64	107.25 ± 6.34	117.77 ± 11.70
Female			
6-Month Interim	85.43 ± 4.22	83.05 ± 4.44	76.36 ± 3.45
11-Month Interim	87.89 ± 3.95	88.18 ± 3.26	78.78 ± 3.81
18-Month Interim	87.14 ± 2.71	73.54 ± 3.02**	76.83 ± 2.29**
24-Month Interim	83.87 ± 5.04	79.64 ± 5.29	82.07 ± 5.95

** Significantly different (P=0.01) from the control by Dunn's or Shirley's test
[a] Units are presented as mL/min; ratio is (dosed group mean/control group mean)×100

TABLE F14
Minute Volume/Kilogram Body Weight of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	266.0 ± 7.0	277.7 ± 12.8	285.1 ± 9.5
11-Month Interim	247.9 ± 5.9	254.5 ± 7.2	247.6 ± 8.2
18-Month Interim	219.4 ± 4.6	206.8 ± 8.2	226.8 ± 10.5
24-Month Interim	229.5 ± 12.7	256.9 ± 14.8	319.9 ± 38.1
Female			
6-Month Interim	408.7 ± 23.3	381.7 ± 19.5	362.7 ± 19.2
11-Month Interim	365.0 ± 18.9	359.3 ± 18.1	330.1 ± 20.7
18-Month Interim	286.2 ± 11.0	250.6 ± 7.6	291.6 ± 17.7
24-Month Interim	276.9 ± 17.4	282.5 ± 21.4	328.8 ± 57.7

[a] Units are presented as mL/min/kg; ratio is (dosed group mean/control group mean)×100

TABLE F15
Residual Volume of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	2.90 ± 0.21	2.99 ± 0.17	2.64 ± 0.11
11-Month Interim	2.06 ± 0.17	1.63 ± 0.10	1.70 ± 0.16
18-Month Interim	1.96 ± 0.15	1.74 ± 0.13	1.98 ± 0.16
24-Month Interim	3.23 ± 0.48	2.83 ± 0.19	2.20 ± 0.32
Female			
6-Month Interim	2.18 ± 0.14	2.39 ± 0.22	2.47 ± 0.15
11-Month Interim	1.22 ± 0.15	1.25 ± 0.17	1.65 ± 0.14
18-Month Interim	1.28 ± 0.11	1.52 ± 0.13	1.83 ± 0.13**
24-Month Interim	1.68 ± 0.11	1.72 ± 0.23	1.73 ± 0.19

** Significantly different (P≤0.01) from the control by Dunn's or Shirley's test
[a] Units are presented as mL; ratio is (dosed group mean/control group mean)×100

TABLE F16
Residual Volume/Total Lung Capacity of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	0.146 ± 0.009	0.154 ± 0.009	0.137 ± 0.004
11-Month Interim	0.102 ± 0.008	0.088 ± 0.005	0.096 ± 0.008
18-Month Interim	0.097 ± 0.007	0.092 ± 0.007	0.121 ± 0.010
24-Month Interim	0.157 ± 0.019	0.140 ± 0.010	0.133 ± 0.011
Female			
6-Month Interim	0.153 ± 0.009	0.163 ± 0.013	0.179 ± 0.011
11-Month Interim	0.091 ± 0.010	0.096 ± 0.013	0.137 ± 0.011*
18-Month Interim	0.091 ± 0.007	0.120 ± 0.010*	0.160 ± 0.009**
24-Month Interim	0.113 ± 0.007	0.125 ± 0.016	0.151 ± 0.005

* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test
** P≤0.01
[a] Units are presented as mL/mL; ratio is (dosed group mean/control group mean)×100

TABLE F17
Vital Capacity of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	16.96 ± 0.49	16.49 ± 0.44	16.61 ± 0.32
11-Month Interim	18.01 ± 0.27	16.82 ± 0.37*	15.97 ± 0.42**
18-Month Interim	18.35 ± 0.45	17.15 ± 0.38	14.36 ± 0.51**
24-Month Interim	17.27 ± 0.48	17.35 ± 0.34	14.27 ± 1.26
Female			
6-Month Interim	12.02 ± 0.22	12.17 ± 0.20	11.33 ± 0.28
11-Month Interim	12.06 ± 0.20	11.68 ± 0.18	10.40 ± 0.25**
18-Month Interim	12.66 ± 0.21	11.14 ± 0.31**	9.61 ± 0.26**
24-Month Interim	13.15 ± 0.27	11.99 ± 0.32*	9.77 ± 0.90**

* Significantly different ($P \leq 0.05$) from the control by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Units are presented as mL; ratio is (dosed group mean/control group mean)×100

TABLE F18
Vital Capacity/Total Lung Capacity of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	0.854 ± 0.009	0.846 ± 0.009	0.863 ± 0.004
11-Month Interim	0.898 ± 0.008	0.912 ± 0.005	0.904 ± 0.008
18-Month Interim	0.904 ± 0.007	0.909 ± 0.006	0.878 ± 0.010
24-Month Interim	0.843 ± .0.19	0.859 ± 0.010	0.867 ± 0.011
Female			
6-Month Interim	0.847 ± 0.009	0.837 ± 0.013	0.821 ± 0.011
11-Month Interim	0.908 ± 0.010	0.905 ± 0.012	0.862 ± 0.010*
18-Month Interim	0.908 ± 0.007	0.879 ± 0.010*	0.841 ± 0.009**
24-Month Interim	0.886 ± 0.007	0.874 ± 0.016	0.849 ± 0.005

* Significantly different ($P \leq 0.05$) from the control by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Units are presented as mL/mL; ratio is (dosed group mean/control group mean)×100

TABLE F19
Forced Vital Capacity of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	17.88 ± 0.40	17.15 ± 0.45	17.38 ± 0.41
11-Month Interim	19.03 ± 0.38	18.07 ± 0.43*	17.25 ± 0.45*
18-Month Interim	19.45 ± 0.45	17.92 ± 0.34*	15.28 ± 0.56**
24-Month Interim	17.27 ± 0.61	17.53 ± 0.46	14.90 ± 1.08
Female			
6-Month Interim	12.53 ± 0.33	12.38 ± 0.26	11.27 ± 0.33*
11-Month Interim	12.86 ± 0.25	12.44 ± 0.26	11.22 ± 0.25**
18-Month Interim	13.39 ± 0.24	11.91 ± 0.28**	10.24 ± 0.27**
24-Month Interim	13.08 ± 0.30	12.33 ± 0.33	10.03 ± 0.93**

* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test
** P≤0.01
[a] Units are presented as mL; ratio is (dosed group mean/control group mean)×100

TABLE F20
Forced Vital Capacity/Kilogram Body Weight of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	46.48 ± 0.61	45.32 ± 1.18	47.32 ± 1.25
11-Month Interim	45.26 ± 0.95	43.22 ± 0.95	42.42 ± 0.89
18-Month Interim	44.00 ± 1.56	40.82 ± 1.01	36.23 ± 1.57**
24-Month Interim	42.85 ± 2.67	42.00 ± 0.93	40.18 ± 2.32
Female			
6-Month Interim	59.78 ± 1.75	57.01 ± 1.49	53.37 ± 1.48*
11-Month Interim	53.35 ± 1.68	50.43 ± 1.16	46.69 ± 0.90**
18-Month Interim	43.95 ± 1.18	40.76 ± 1.08	38.75 ± 2.17**
24-Month Interim	43.23 ± 1.51	43.87 ± 2.08	38.85 ± 0.48

* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test
** P≤0.01
[a] Units are presented as mL/kg; ratio is (dosed group mean/control group mean)×100

TABLE F21
Functional Residual Capacity of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	4.48 ± 0.25	4.48 ± 0.22	4.17 ± 0.10
11-Month Interim	3.34 ± 0.24	3.16 ± 0.09	3.19 ± 0.12
18-Month Interim	3.24 ± 0.16	3.07 ± 0.11	3.53 ± 0.14
24-Month Interim	4.53 ± 0.52	3.98 ± 0.24	4.37 ± 0.59
Female			
6-Month Interim	3.51 ± 0.12	3.72 ± 0.16	3.57 ± 0.15
11-Month Interim	2.78 ± 0.12	2.74 ± 0.10	2.87 ± 0.14
18-Month Interim	2.47 ± 0.08	2.82 ± 0.12*	3.17 ± 0.14**
24-Month Interim	3.07 ± 0.13	3.31 ± 0.26	3.27 ± 0.18

* Significantly different ($P \leq 0.05$) from the control by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Units are presented as mL; ratio is (dosed group mean/control group mean)×100

TABLE F22
Functional Residual Capacity/Total Lung Capacity of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	0.226 ± 0.012	0.230 ± 0.009	0.217 ± 0.006
11-Month Interim	0.166 ± 0.011	0.172 ± 0.006	0.181 ± 0.007
18-Month Interim	0.159 ± 0.006	0.163 ± 0.005	0.217 ± 0.008**
24-Month Interim	0.220 ± 0.020	0.197 ± 0.012	0.268 ± 0.042
Female			
6-Month Interim	0.248 ± 0.008	0.255 ± 0.009	0.258 ± 0.008
11-Month Interim	0.209 ± 0.008	0.212 ± 0.006	0.238 ± 0.010*
18-Month Interim	0.177 ± 0.007	0.223 ± 0.010**	0.277 ± 0.010**
24-Month Interim	0.207 ± 0.009	0.240 ± 0.016	0.287 ± 0.021*

* Significantly different ($P \leq 0.05$) from the control by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Units are presented as mL/mL; ratio is (dosed group mean/control group mean)×100

TABLE F23
Total Pulmonary Resistance of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
18-Month Interim	0.075 ± 0.014	0.096 ± 0.009	0.120 ± 0.009*
24-Month Interim	0.110 ± 0.025	0.087 ± 0.028	0.067 ± 0.020
Female			
18-Month Interim	0.130 ± 0.012	0.131 ± 0.016	0.180 ± 0.010*
24-Month Interim	0.138 ± 0.020	0.131 ± 0.014	0.150 ± 0.035

* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test
[a] Units are presented as cm H_2O/mL/second; ratio is (dosed group mean/control group mean)×100

TABLE F24
Maximum Quasistatic Compliance of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	1.97 ± 0.15	1.84 ± 0.12	2.01 ± 0.13
11-Month Interim	2.32 ± 0.10	1.92 ± 0.12*	1.91 ± 0.09*
18-Month Interim	2.35 ± 0.07	2.09 ± 0.16	1.57 ± 0.07**
24-Month Interim	2.00 ± 0.30	2.01 ± 0.11	1.48 ± 0.20
Female			
6-Month Interim	1.37 ± 0.11	1.47 ± 0.11	1.37 ± 0.08
11-Month Interim	1.273 ± 0.062	1.276 ± 0.033	0.968 ± 0.057**
18-Month Interim	1.704 ± 0.108	1.123 ± 0.050**	0.908 ± 0.068**
24-Month Interim	1.538 ± 0.055	1.263 ± 0.062**	0.883 ± 0.093**

* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test
** P≤0.01
[a] Units are presented as mL/cm H_2O; ratio is (dosed group mean/control group mean)×100

TABLE F25
Quasistatic Chord Compliance of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	1.18 ± 0.05	1.16 ± 0.04	1.17 ± 0.03
11-Month Interim	1.34 ± 0.02	1.20 ± 0.04*	1.15 ± 0.04**
18-Month Interim	1.343 ± 0.037	1.205 ± 0.040*	0.982 ± 0.037**
24-Month Interim	1.167 ± 0.104	1.220 ± 0.035	0.890 ± 0.124
Female			
6-Month Interim	0.824 ± 0.030	0.895 ± 0.091	0.802 ± 0.024
11-Month Interim	0.841 ± 0.020	0.809 ± 0.016	0.684 ± 0.025**
18-Month Interim	0.879 ± 0.019	0.749 ± 0.027**	0.607 ± 0.030**
24-Month Interim	0.883 ± 0.035	0.764 ± 0.024*	0.573 ± 0.084**

* Significantly different ($P \leq 0.05$) from the control by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Units are presented as mL/cm H_2O; ratio is (dosed group mean/control group mean)×100

TABLE F26
Dynamic Compliance of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	0.546 ± 0.053	0.575 ± 0.043	0.536 ± 0.058
11-Month Interim	0.748 ± 0.041	0.647 ± 0.048	0.687 ± 0.046
18-Month Interim	0.990 ± 0.080	0.741 ± 0.043*	0.685 ± 0.050**
24-Month Interim	0.930 ± 0.173	0.987 ± 0.130	1.173 ± 0.186
Female			
6-Month Interim	0.399 ± 0.029	0.445 ± 0.032	0.380 ± 0.034
11-Month Interim	0.492 ± 0.024	0.426 ± 0.027*	0.393 ± 0.020**
18-Month Interim	0.618 ± 0.053	0.527 ± 0.027	0.372 ± 0.025**
24-Month Interim	0.650 ± 0.065	0.618 ± 0.045	0.377 ± 0.077*

* Significantly different ($P \leq 0.05$) from the control by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Units are presented as mL/cm H_2O; ratio is (dosed group mean/control group mean)×100

TABLE F27
Peak Expiratory Flow of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	139.9 ± 1.9	138.7 ± 2.8	132.5 ± 4.0
11-Month Interim	136.6 ± 1.4	133.5 ± 4.5	132.9 ± 2.0
18-Month Interim	132.2 ± 1.2	132.3 ± 0.7	129.5 ± 0.6**
24-Month Interim	126.1 ± 2.7	124.5 ± 1.9	124.0 ± 1.0
Female			
6-Month Interim	120.1 ± 8.7	122.3 ± 6.6	113.5 ± 5.7
11-Month Interim	125.3 ± 4.3	123.9 ± 4.9	123.2 ± 2.1
18-Month Interim	120.6 ± 3.0	113.2 ± 2.3	114.3 ± 2.5
24-Month Interim	117.1 ± 2.5	116.7 ± 3.4	110.1 ± 4.7

** Significantly different (P≤0.01) from the control by Dunn's or Shirley's test
[a] Units are presented as mL/second; ratio is (dosed group mean/control group mean)×100

TABLE F28
Peak Expiratory Flow/Forced Vital Capacity of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	7.85 ± 0.18	8.12 ± 0.22	7.63 ± 0.16
11-Month Interim	7.21 ± 0.18	7.44 ± 0.33	7.74 ± 0.20
18-Month Interim	6.82 ± 0.15	7.40 ± 0.14*	8.57 ± 0.29**
24-Month Interim	7.31 ± 0.14	7.13 ± 0.21	8.40 ± 0.52
Female			
6-Month Interim	9.56 ± 0.62	9.82 ± 0.35	10.08 ± 0.47
11-Month Interim	9.73 ± 0.22	9.95 ± 0.31	11.01 ± 0.23**
18-Month Interim	9.02 ± 0.20	9.57 ± 0.37	11.21 ± 0.32**
24-Month Interim	8.96 ± 0.22	9.47 ± 0.19	11.16 ± 1.13**

* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test
** P≤0.01
[a] Units are presented as mL/second/mL; ratio is (dosed group mean/control group mean)×100

TABLE F29
Expiratory Flow 10% Forced Vital Capacity of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	28.22 ± 2.04	24.20 ± 1.77	19.60 ± 2.67*
11-Month Interim	26.33 ± 1.82	20.80 ± 1.14*	21.60 ± 1.50
18-Month Interim	19.00 ± 1.87	18.00 ± 1.61	20.70 ± 1.17
24-Month Interim	11.33 ± 1.20	18.67 ± 1.50	18.33 ± 1.76
Female			
6-Month Interim	17.40 ± 2.88	18.10 ± 3.10	16.60 ± 2.68
11-Month Interim	19.20 ± 2.36	19.50 ± 1.97	23.30 ± 2.29
18-Month Interim	19.67 ± 1.62	19.00 ± 1.45	21.78 ± 0.66
24-Month Interim	12.67 ± 1.65	18.44 ± 1.51*	17.00 ± 2.52

* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test
[a] Units are presented as mL/second; ratio is (dosed group mean/control group mean)×100

TABLE F30
Expiratory Flow 10% Forced Vital Capacity/Forced Vital Capacity of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	1.58 ± 0.11	1.41 ± 0.09	1.13 ± 0.16*
11-Month Interim	1.39 ± 0.10	1.16 ± 0.08	1.27 ± 0.11
18-Month Interim	0.986 ± 0.106	1.002 ± 0.085	1.372 ± 0.085*
24-Month Interim	0.661 ± 0.085	1.057 ± 0.065*	1.256 ± 0.188*
Female			
6-Month Interim	1.37 ± 0.21	1.43 ± 0.23	1.45 ± 0.22
11-Month Interim	1.47 ± 0.17	1.55 ± 0.14	2.07 ± 0.19**
18-Month Interim	1.47 ± 0.13	1.62 ± 0.15	2.14 ± 0.09**
24-Month Interim	0.959 ± 0.109	1.488 ± 0.102*	1.693 ± 0.170*

* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test
** P≤0.01
[a] Units are presented as mL/second/mL; ratio is (dosed group mean/control group mean)×100

TABLE F31
Expiratory Flow 25% Forced Vital Capacity of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	63.56 ± 3.30	55.00 ± 5.57	44.30 ± 6.59*
11-Month Interim	62.00 ± 2.89	60.40 ± 3.46	59.30 ± 3.36
18-Month Interim	50.50 ± 2.57	54.20 ± 2.45	62.20 ± 2.80**
24-Month Interim	47.00 ± 2.89	51.33 ± 3.97	60.00 ± 3.79
Female			
6-Month Interim	44.30 ± 7.73	41.20 ± 7.14	35.60 ± 5.59
11-Month Interim	50.40 ± 5.68	43.00 ± 5.69	54.60 ± 4.01
18-Month Interim	52.33 ± 4.57	42.56 ± 4.76	49.00 ± 3.67
24-Month Interim	40.67 ± 3.80	49.33 ± 6.17	46.00 ± 12.49

* Significantly different ($P \leq 0.05$) from the control by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Units are presented as mL/second; ratio is (dosed group mean/control group mean)×100

TABLE F32
Expiratory Flow 25% Forced Vital Capacity/Forced Vital Capacity of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	3.56 ± 0.19	3.21 ± 0.31	2.54 ± 0.37
11-Month Interim	3.26 ± 0.14	3.35 ± 0.20	3.47 ± 0.24
18-Month Interim	2.61 ± 0.15	3.03 ± 0.14*	4.14 ± 0.27**
24-Month Interim	2.72 ± 0.07	2.92 ± 0.20	4.06 ± 0.35*
Female			
6-Month Interim	3.50 ± 0.59	3.25 ± 0.53	3.10 ± 0.43
11-Month Interim	3.88 ± 0.42	3.43 ± 0.44	4.88 ± 0.37
18-Month Interim	3.91 ± 0.34	3.60 ± 0.44	4.75 ± 0.27
24-Month Interim	3.10 ± 0.24	3.95 ± 0.44	4.66 ± 1.28

* Significantly different ($P \leq 0.05$) from the control by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Units are presented as mL/second/mL; ratio is (dosed group mean/control group mean)×100

TABLE F33
Expiratory Flow 50% Forced Vital Capacity of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	111.33 ± 7.11	94.00 ± 7.61	78.70 ± 10.05*
11-Month Interim	111.7 ± 4.4	100.1 ± 7.1	102.1 ± 6.2
18-Month Interim	98.75 ± 6.00	97.10 ± 3.59	107.70 ± 5.25
24-Month Interim	99.33 ± 10.17	92.33 ± 4.47	94.67 ± 9.02
Female			
6-Month Interim	75.30 ± 11.98	73.90 ± 10.54	66.00 ± 8.52
11-Month Interim	85.50 ± 8.87	78.00 ± 10.09	94.10 ± 5.57
18-Month Interim	93.00 ± 8.40	76.11 ± 9.60	87.67 ± 6.91
24-Month Interim	86.50 ± 7.12	85.89 ± 10.40	83.67 ± 23.90

* Significantly different ($P \leq 0.05$) from the control by Dunn's or Shirley's test
[a] Units are presented as mL/second; ratio is (dosed group mean/control group mean)×100

TABLE F34
Expiratory Flow 50% Forced Vital Capacity/Forced Vital Capacity of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	6.23 ± 0.39	5.50 ± 0.47	4.49 ± 0.55*
11-Month Interim	5.86 ± 0.18	5.55 ± 0.40	5.95 ± 0.40
18-Month Interim	5.08 ± 0.30	5.43 ± 0.21	7.18 ± 0.50**
24-Month Interim	5.73 ± 0.44	5.30 ± 0.36	6.38 ± 0.62
Female			
6-Month Interim	5.95 ± 0.90	5.85 ± 0.77	5.79 ± 0.67
11-Month Interim	6.58 ± 0.62	6.21 ± 0.77	8.39 ± 0.48*
18-Month Interim	6.92 ± 0.59	6.48 ± 0.90	8.49 ± 0.54
24-Month Interim	6.63 ± 0.55	6.88 ± 0.77	8.50 ± 2.50

* Significantly different ($P \leq 0.05$) from the control by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Units are presented as mL/second/mL; ratio is (dosed group mean/control group mean)×100

TABLE F35
Mean Midexpiratory Flow of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	101.90 ± 5.20	89.30 ± 7.34	74.27 ± 9.38*
11-Month Interim	102.52 ± 3.54	94.92 ± 6.02	94.11 ± 4.51
18-Month Interim	93.12 ± 3.99	91.41 ± 2.81	98.44 ± 3.67
24-Month Interim	87.13 ± 6.27	87.78 ± 3.74	90.33 ± 7.07
Female			
6-Month Interim	71.07 ± 12.01	70.72 ± 10.66	60.65 ± 7.99
11-Month Interim	81.38 ± 7.94	73.24 ± 9.19	87.91 ± 5.04
18-Month Interim	85.98 ± 6.80	69.51 ± 7.53	81.79 ± 5.58
24-Month Interim	78.28 ± 5.27	79.94 ± 9.44	75.13 ± 19.66

* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test
[a] Units are presented as mL/second; ratio is (dosed group mean/control group mean)×100

TABLE F36
Mean Midexpiratory Flow/Forced Vital Capacity of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	5.71 ± 0.30	5.23 ± 0.44	4.24 ± 0.51
11-Month Interim	5.39 ± 0.16	5.27 ± 0.35	5.49 ± 0.32
18-Month Interim	4.78 ± 0.13	5.11 ± 0.18	6.55 ± 0.39**
24-Month Interim	5.04 ± 0.24	5.03 ± 0.29	6.10 ± 0.56
Female			
6-Month Interim	5.62 ± 0.91	5.59 ± 0.78	5.31 ± 0.62
11-Month Interim	6.27 ± 0.56	5.83 ± 0.70	7.85 ± 0.45*
18-Month Interim	6.41 ± 0.48	5.90 ± 0.72	7.94 ± 0.41
24-Month Interim	5.99 ± 0.39	6.40 ± 0.69	7.65 ± 2.13

* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test
** P≤0.01
[a] Units are presented as mL/second/mL; ratio is (dosed group mean/control group mean)×100

TABLE F37
Carbon Monoxide Diffusing Capacity of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	0.364 ± 0.014	0.347 ± 0.008	0.336 ± 0.010
11-Month Interim	0.400 ± 0.010	0.373 ± 0.010	0.331 ± 0.020**
18-Month Interim	0.338 ± 0.022	0.301 ± 0.015	0.235 ± 0.009**
24-Month Interim	0.303 ± 0.027	0.288 ± 0.011	0.177 ± 0.035*
Female			
6-Month Interim	0.238 ± 0.012	0.241 ± 0.008	0.213 ± 0.010
11-Month Interim	0.233 ± 0.008	0.231 ± 0.005	0.190 ± 0.003**
18-Month Interim	0.233 ± 0.010	0.207 ± 0.009	0.137 ± 0.011**
24-Month Interim	0.198 ± 0.007	0.183 ± 0.006	0.113 ± 0.017**

* Significantly different ($P \le 0.05$) from the control by Dunn's or Shirley's test
** $P \le 0.01$
[a] Units are presented as mL/minute/mm Hg; ratio is (dosed group mean/control group mean)×100

TABLE F38
Carbon Monoxide Diffusing Capacity/Lung Volume of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	0.020 ± 0.001	0.020 ± 0.000	0.019 ± 0.000
11-Month Interim	0.021 ± 0.000	0.021 ± 0.001	0.019 ± 0.001*
18-Month Interim	0.017 ± 0.001	0.025 ± 0.008	0.014 ± 0.001*
24-Month Interim	0.015 ± 0.002	0.015 ± 0.001	0.010 ± 0.002*
Female			
6-Month Interim	0.019 ± 0.001	0.019 ± 0.001	0.017 ± 0.001
11-Month Interim	0.018 ± 0.001	0.019 ± 0.000	0.017 ± 0.000*
18-Month Interim	0.017 ± 0.001	0.016 ± 0.001	0.012 ± 0.001**
24-Month Interim	0.013 ± 0.001	0.013 ± 0.001	0.009 ± 0.001

* Significantly different ($P \le 0.05$) from the control by Dunn's or Shirley's test
** $P \le 0.01$
[a] Ratio is (dosed group mean/control group mean)×100

TABLE F39
Carbon Monoxide Diffusing Capacity/Kilogram Body Weight of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	0.949 ± 0.039	0.917 ± 0.017	0.914 ± 0.026
11-Month Interim	0.951 ± 0.021	0.892 ± 0.021	0.821 ± 0.043**
18-Month Interim	0.759 ± 0.043	0.683 ± 0.029	0.554 ± 0.016**
24-Month Interim	0.749 ± 0.056	0.691 ± 0.025	0.465 ± 0.062*
Female			
6-Month Interim	1.13 ± 0.05	1.11 ± 0.04	1.01 ± 0.04
11-Month Interim	0.968 ± 0.045	0.939 ± 0.033	0.792 ± 0.019**
18-Month Interim	0.766 ± 0.034	0.705 ± 0.028	0.502 ± 0.028**
24-Month Interim	0.656 ± 0.031	0.650 ± 0.027	0.435 ± 0.036*

* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test
** P≤0.01
[a] Units are presented as mL/minute/mm Hg/kg; ratio is (dosed group mean/control group mean)×100

TABLE F40
Percent Forced Vital Capacity Expired in 0.1 Second of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	61.11 ± 1.52	59.80 ± 2.15	53.90 ± 2.64
11-Month Interim	58.22 ± 0.98	57.40 ± 2.74	60.30 ± 1.63
18-Month Interim	55.00 ± 0.63	58.30 ± 0.90*	66.50 ± 2.13**
24-Month Interim	58.67 ± 1.20	57.00 ±1.71	64.00 ± 2.89
Female			
6-Month Interim	62.80 ± 5.17	64.20 ± 3.82	63.40 ± 3.86
11-Month Interim	67.00 ± 2.82	65.20 ± 3.61	75.50 ± 1.78*
18-Month Interim	66.44 ± 2.60	64.56 ± 3.57	75.78 ± 1.56*
24-Month Interim	65.83 ± 2.09	66.78 ± 3.31	73.00 ± 9.17

* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test
** P≤0.01
[a] Units are presented as percent forced vital capacity; ratio is (dosed group mean/control group mean)×100

TABLE F41
Slope III of N_2 Washout of Rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	0.400 ± 0.023	0.431 ± 0.037	0.481 ± 0.049
11-Month Interim	0.449 ± 0.019	0.446 ± 0.037	0.437 ± 0.040
18-Month Interim	0.393 ± 0.037	0.361 ± 0.035	0.555 ± 0.041*
24-Month Interim	0.627 ± 0.077	0.438 ± 0.045	0.597 ± 0.083
Female			
6-Month Interim	0.587 ± 0.059	0.528 ± 0.049	0.596 ± 0.042
11-Month Interim	0.704 ± 0.027	0.735 ± 0.029	0.813 ± 0.076
18-Month Interim	0.601 ± 0.053	0.699 ± 0.074	1.008 ± 0.087**
24-Month Interim	0.535 ± 0.040	0.580 ± 0.071	1.520 ± 0.409*

* Significantly different ($P \leq 0.05$) from the control by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Units are presented as percent N_2/mL; ratio is (dosed group mean/control group mean)×100

APPENDIX G
LUNG BURDEN AND LUNG BIOCHEMISTRY IN MICE

METHODS

Lung Burden

Lung talc burden was measured to determine the relationship between the exposure concentration and the amount of talc deposited and retained within the pulmonary region of the respiratory tract. The method used for determination of talc in the lungs of rats and mice has been published (Hanson *et al.*, 1985). Lung burdens of talc were determined on the left lung of 4 male and 4 female mice from each exposure group sacrificed at 27, 52, and 79 weeks after the start of exposure. At 103 to 104 weeks, lung burdens were determined on the left lungs of two mice from the biochemistry group. The analysis was based on determination of acid insoluble magnesium in the lung. MRI reported that the value for the magnesium was 19.33% for batch 02, and 19.47% for batch 03. The values reported by MRI and the results of the analysis at LITRI were close to the theoretical value of magnesium for talc (19.22%). Since mice sacrificed at 27, 52, and 79 weeks had been exposed to only batch 02 of talc, 19.33% magnesium was used to calculate quantity of talc for these mice. Since batch 03 was used for the last 4 months of exposure, and lung burdens of mice after 103 to 104 weeks of exposure talc would be expected to contain substantial amounts of batch 03 talc, 19.47% magnesium was used to calculate quantity of talc in lungs for these mice.

All operations in conjunction with the tissue analysis for talc were done with talc-free gloves. Left lung lobes were weighed at necropsy and stored frozen (-20° C) until used. Lungs were homogenized using water and the proteins precipitated with 70% perchloric acid. The individual samples were filtered and washed with 5% trichloroacetic acid (TCA) to remove perchlorates. Washing continued until magnesium levels in the wash were within 10% of levels in the TCA solution ($\leq$ 0.03 ppm magnesium). Filters and tissue residues were placed in 15 mL porcelain crucibles, dried slowly (200° C), and then ashed at 600° C for 1 hour. Ashed samples were transferred to Teflon beakers using 2 mL HCl and evaporated to dryness. Samples were digested in hydrofluoric acid (HF), and the HF evaporated. Additional HF was added and reevaporated. Sulfuric acid was added to remove trace HF, and samples were diluted with distilled water and analyzed for magnesium by atomic absorbance (Perkin Elmer, Model 306, Atomic Absorption Spectrophotometer) with a magnesium hollow cathode lamp and an air acetylene flame (Hanson *et al.*, 1985).

Lung Biochemistry

In this study, bronchoalveolar lavage (BAL) fluid enzyme activity and cell numbers were measured as biochemical and cytological indicators of pulmonary injury from inhalation of talc. Four mice of each sex from each exposure group were sacrificed at 27, 52, and 79 weeks, and all remaining lung toxicology mice were sacrificed at 103 to 104 weeks. Numbers of animals at each sacrifice are shown below.

Mice were anesthetized with halothane and sacrificed by exsanguination from the abdominal aorta or renal artery. The heart and lung block were removed. Mice were given endobronchial saline lavage (3 to 4 mL total volume in four, 0.75 to 1.0 mL washes) and the BAL fluid centrifuged at 300 × G to separate the cells from the supernatant fluid.

At all sacrifices, biochemical analyses were done on lavage fluid from single mice. At the 103 to 104 week terminal sacrifice where lung burden measurements were also performed on the left lung lobes, mouse lavage fluids were paired (from 2 mice) to obtain sufficient cells for the analyses and paired mouse lung tissue samples (from 2 mice) were analyzed to obtain sufficient lung tissue for collagen analyses.

Airway Fluid Enzymes and Cytology

In this study, BAL fluid was analyzed to determine degree of:

1) Cell injury as indicated by quantities of BAL fluid lactate dehydrogenase (LDH).
2) Chronic inflammatory response as indicated by presence of increased numbers of polymorphonuclear leukocytes (PMN) and pulmonary alveolar macrophages (AM) as well as increased BAL fluid protein and alkaline phosphatase activity.

3) Lysosomal activation as indicated by quantities of BAL fluid ß-glucuronidase and acid proteinase. Elevated quantities of these enzymes have been observed in BAL fluid from rodents exposed to particulates. These enzymes may be associated with the breakdown of necrotic tissues.
4) Response to oxidant injury as indicated by increased quantities of glutathione reductase and peroxidase activity.

The supernatant fluid was analyzed for the activities of ß-glucuronidase, LDH, glucose-6-phosphate dehydrogenase, alkaline phosphatase, glutathione reductase, and glutathione peroxidase by spectrophotometric, kinetic, and enzymatic techniques. Acid proteinase was measured by release of radiolabeled globin from the trichloroacetic acid precipitatible protein substrate, and total protein was analyzed colorimetrically (Henderson *et al.*, 1985). ß-Glucuronidase was not performed at 27-week interim evaluation, but was performed at all other sacrifice times.

Numbers of total nucleated cells recovered in lavage fluid were determined on each sample using a cell counter (Coulter Electronics, Hileah, FL) or a hemocytometer. Cytocentrifuge preparations of resuspended cells were made, stained with Wrights stain (Diff-Quik, Curtin Matheson Scientific, Denver, CO) and differential cell counts were determined. At the 27, 52, and 79 week interim sacrifices, analyses were done on individual mice.

Alveolar macrophages (AM) were recovered from BAL fluid of the same mice as described above. Cells (0.5×10^6) in Roswell Park Memorial Institute (RPMI) culture medium were pelleted by centrifugation and the supernatant RPMI removed. Cells were resuspended in 1 mL of a 1% suspension of IgG antibody-sensitized sheep red blood cells (SRBC) in RPMI 1640. The antibody sensitized SRBC were made as previously described (Harmsen and Jeska, 1980). The subagglutinating titer of heat-inactivated rabbit anti-SRBC serum was used to sensitize the SRBC. The AM and SRBC suspensions were incubated at 37° C for 1 hour in a humidified atmosphere of 5% CO_2 in air. The AM and SRBC were sedimented by centrifugation and the supernatant discarded. Unphagocytized SRBC were removed by lysing the RBC with water for 30 seconds. The lysing of unphagocytized SRBC was stopped by the addition of an equal volume of saline and cytocentrifuge preparations were made. The slides were stained with a rapid Wright's stain (Diff-Quik, American Scientific Products, McGaw Park, IL) and the number of AM phagocytizing 0, 1, 2, 3 to 4, and > 4 SRBC was determined by light microscopy. Three fields of 100 cells per preparation were counted. Viability of macrophages was not determined at the 27, 52, and 79 week sacrifices because the small number of cells recovered from these mice lungs precluded the measurement of cell viability. Viability determination of macrophages was made on macrophages obtained at the final sacrifice because sufficient numbers of cells were generally available at this time.

Lung Tissue Collagen and Proteinase

At 27-, 52-, and 79-week sacrifices, collagen content of lungs and lavage fluid was measured. At the 103 to 104 week sacrifice, additional collagen metabolism and protein synthesis measurements were made on survivors from each group. Proteinase activities were measured at all sacrifice times.

The supernatant BAL fluid was analyzed for hydroxyproline and acid proteinase. Lung tissue and bronchoalveolar lavage (BAL) fluid samples were hydrolyzed with 6N HCl at 110° C for approximately 18 hours to convert proteins to their individual amino acids. Collagen quantity was measured and multiplied by 7.46 to convert BAL or lung tissue hydroxyproline content to BAL or lung tissue collagen content, taking into account that collagen is approximately 13% hydroxyproline by weight (Neuman and Logan, 1950).

Additional collagen metabolism measurements were made on the mice sacrificed after 103 to 104 weeks of talc exposure to further define collagen metabolism. Approximately 2 to 3 hours prior to sacrifice, ^{14}C-proline (0.1 μCi/g body weight) was injected intraperitoneally to estimate collagen and protein synthesis. Radioactive proline and hydroxyproline were quantitated in lung hydrolysate. Following this,

the radioactive proline and hydroxyproline quantities were used to calculate the noncollagenous protein synthesis, and the collagen production.

Noncollagenous protein synthesis was indicated as total ^{14}C-proline incorporation into lung tissue minus the incorporation into lung tissue which was related to collagen synthesis. The radioactive proline in collagen was assumed to be equal to the radioactive hydroxyproline, thus, incorporation into collagen was calculated as twice the radioactive hydroxyproline. Collagen production (% of newly synthesized protein that was collagen) was calculated as the percent incorporation of proline into collagen constituted of the total incorporation of proline into all proteins, and adjusted for the 5.4-fold difference in the content of total amino acids (proline and hydroxyproline) between collagen and noncollagenous protein (Pickrell *et al.*, 1987).

At each sacrifice time, lung tissue proteinase activity was measured as the release of ^{14}C-leucine from prelabeled globin at pH 4.2 and 7.5 (Gregory and Pickrell, 1982; Harkema *et al.*, 1984; Pickrell *et al.*, 1987). Acid proteinase activity was inhibited by leupeptin to indicate either cathepsin B (inhibited) or cathepsin D (not inhibited)-like activity. Neutral proteinase activity was inhibited by 1, 10-phenanthroline to indicate either macrophage elastase (inhibited) or neutrophil elastase-cathepsin G (not inhibited)-like activity.

TABLE G1
Number of Mice Evaluated for Lung Talc Burden and Lung Biochemistry

	Male			Female		
	0 mg/m³	6 mg/m³	18 mg/m³	0 mg/m³	6 mg/m³	18 mg/m³
Lung Burden						
6-Month Interim	–[a]	2	4	–	4	4
12-Month Interim	–	4	4	–	4	4
18-Month Interim	–	2	1	–	4	3
24-Month Interim	–	8	6	–	6	5
Lung Biochemistry						
6-Month Interim	4	4	4	4	4	4
12-Month Interim	4	4	4	4	4	4
18-Month Interim	4	4	4	4	4	4
24-Month Interim	9	8	6	7	6	5

[a] Lung burden not measured in 0 mg/m³ mice

TABLE G2
Lung Talc Burden (Normalized to Control Lung Weight) of Mice[a]

	6 months	12 months	18 months	24 months
Male				
0 mg/m³	–[b]	–	–	–
6 mg/m³	0.415 ± 0.114	1.084 ± 0.130	0.426 ± 0.040	2.973 ± 0.762
18 mg/m³	1.41 ± 0.29	9.00 ± 1.45	8.36	19.73 ± 4.03
Female				
0 mg/m³	–	–	–	–
6 mg/m³	0.524 ± 0.056	0.707 ± 0.170	1.387 ± 0.178	2.667 ± 0.720
18 mg/m³	1.35 ± 0.24	6.17 ± 1.39	7.83 ± 1.36	20.05 ± 0.98

a Units are presented as mg talc/g control lung.
b Not examined

TABLE G3
Lung Talc Burden (Normalized to Exposure Concentration) of Mice[a]

	Male		Female	
	6 mg/m³	18 mg/m³	6 mg/m³	18 mg/m³
6-Month Interim	0.069 ± 0.019	0.078 ± 0.016	0.087 ± 0.009	0.075 ± 0.013
12-Month Interim	0.181 ± 0.022	0.500 ± 0.081*	0.118 ± 0.028	0.343 ± 0.077*
18-Month Interim	0.071 ± 0.007	0.464[b]	0.231 ± 0.030	0.435 ± 0.075
24-Month Interim	0.496 ± 0.127	1.096 ± 0.224*	0.445 ± 0.120	1.114 ± 0.055*

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
a Units are presented as mg talc/g control lung/mg/m³
b n=1; no statistic calculated

TABLE G4
Bronchoalveolar Lavage Fluid Enzymes of Mice at the 6-Month Interim Evaluation

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
Lactate dehydrogenase[a]	1,408 ± 658	1,317 ± 106	2,107 ± 336
Glutathione reductase	148.4 ± 33.8	123.3 ± 28.3	227.2 ± 65.6
Total protein[b]	3.57 ± 0.89	1.92 ± 0.70	6.24 ± 1.23
Female			
Lactate dehydrogenase	1,988 ± 157	2,351 ± 180	1,400 ± 197
Glutathione reductase	206.8 ± 14.7	166.0 ± 21.3	148.5 ± 29.4
Total protein	2.55 ± 0.53	4.43 ± 0.34	6.89 ± 4.29

[a] Units are presented as mIU/g control lung.
[b] Units are presented as mg/g controls lung.

TABLE G5
Bronchoalveolar Lavage Fluid Enzymes of Mice at the 12-Month Interim Evaluation

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
ß-Glucuronidase[a]	0.188 ± 0.114	0.486 ± 0.346	12.787 ± 3.604*
Lactate dehydrogenase	1,107.6 ± 545	540.2 ± 59.0	1,487.1 ± 456
Glutathione reductase	89.50 ± 11.65	91.67 ± 6.60	302.40 ± 65.15*
Total protein[b]	2.21 ± 0.74	1.56 ± 0.33	6.19 ± 2.63
Female			
ß-Glucuronidase	0.073 ± 0.073	0.413 ± 0.251	9.786 ± 2.271**
Lactate dehyrogenase	1,209.7 ± 305	447.5 ± 76.1	1,805.3 ± 285
Glutathione reductase	113.57 ± 19.78	97.93 ± 14.93	198.65 ± 23.44
Total protein	3.54 ± 1.27	3.61 ± 1.38	4.82 ± 2.88

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Units are presented as mIU/g control lung.
[b] Units are presented as mg/g control lung.

TABLE G6
Bronchoalveolar Lavage Fluid Enzymes of Mice at the 18-Month Interim Evaluation

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
β-Glucuronidase[a]	0.000 ± 0.000	1.344 ± 1.267	9.937 ± 4.196**
Lactate dehydrogenase	434.0 ± 45.7	642.4 ± 119	1,039.9 ± 168**
Glutathione reductase	63.93 ± 14.16	106.38 ± 12.15	217.18 ± 45.29*
Total protein[b]	3.43 ± 0.62	6.23 ± 0.97*	9.45 ± 1.95**
Female			
β-Glucuronidase	4.243 ± 4.203	0.334 ± 0.334	19.064 ± 9.200
Lactate dehydrogenase	501.4 ± 46.9	404.2 ± 97.6	1,217.6 ± 255*
Glutathione reductase	73.19 ± 14.94	71.27 ± 12.11	240.55 ± 44.06*
Total protein	2.96 ± 0.40	3.41 ± 0.92	9.59 ± 1.23*

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Units are presented as mIU/g control lung.
[b] Units are presented as mg/g control lung.

TABLE G7
Bronchoalveolar Lavage Fluid Enzymes of Mice at the 24-Month Interim Evaluation

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
β-Glucuronidase[a]	0.000 ± 0.000	1.811 ± 0.878**	16.571 ± 3.932**
Lactate dehydrogenase	1,769 ± 259	1,439 ± 295	2,965 ± 131*
Glutathione reductase	73.66 ± 9.75	87.55 ± 25.16	229.53 ± 58.46*
Total protein[b]	1.69 ± 0.20	2.34 ± 0.22	4.68 ± 0.70**
Female			
β-Glucuronidase	0.000 ± 0.000	2.624 ± 1.176**	13.778 ± 2.640**
Lactate dehydrogenase	1,082 ± 155	1,596 ± 197*	2,026 ± 279**
Glutathione reductase	68.66 ± 7.42	73.37 ± 13.91	163.46 ± 33.43*
Total protein	1.111 ± 0.310	0.872 ± 0.261	2.228 ± 0.501

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Units are presented as mIU/g control lung.
[b] Units are presented as mg/g control lung.

TABLE G8
Bronchoalveolar Lavage Fluid Cell Populations of Mice at the 6-Month Interim Evaluation[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
Polymorphonucleated cells	0.250 ± 0.250	3.250 ± 1.250	12.000 ± 3.764**
Lymphocytes	0.750 ± 0.750	0.750 ± 0.479	0.000 ± 0.000
Macrophages	92.50 ± 3.23	95.75 ± 1.44	84.75 ± 2.95
Epithelial cells	6.500 ± 3.775	0.250 ± 0.250	3.250 ± 1.250
Female			
Polymorphonuclear cells	0.000 ± 0.000	1.250 ± 0.629*	1.750 ± 0.854**
Lymphocytes	0.000 ± 0.000	1.000 ± 1.000	0.000 ± 0.000
Macrophages	95.00 ± 2.16	94.75 ± 1.44	96.00 ± 1.22
Epithelial cells	5.00 ± 2.16	3.00 ± 1.73	2.25 ± 1.31

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Units are presented as percent of total cells.

TABLE G9
Bronchoalveolar Lavage Fluid Cell Populations of Mice at the 12-Month Interim Evaluation[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
Polymorphonuclear cells	26.75 ± 15.12	7.50 ± 5.85	15.00 ± 14.01
Lymphocytes	0.750 ± 0.250	2.250 ± 1.436	0.333 ± 0.333
Macrophages	70.50 ± 14.56	83.25 ± 6.91	73.33 ± 12.14
Epithelial cells	2.00 ± 1.41	7.00 ± 2.12	11.33 ± 7.36
Female			
Polymorphonuclear cells	1.33 ± 1.33	34.50 ± 10.27*	2.25 ± 0.85
Lymphocytes	1.000 ± 0.577	3.500 ± 1.500	0.000 ± 0.000
Macrophages	92.67 ± 0.33	58.25 ± 11.65	91.00 ± 2.04
Epithelial cells	5.00 ± 1.53	3.75 ± 1.75	6.75 ± 2.84

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
[a] Units are presented as percent of total cells.

TABLE G10
Bronchoalveolar Lavage Fluid Cell Populations of Mice at the 18-Month Interim Evaluation[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
Polymorphonuclear cells	0.250 ± 0.250	8.750 ± 4.404	19.000 ± 6.258*
Lymphocytes	0.000 ± 0.000	0.500 ± 0.500	1.000 ± 0.577
Macrophages	89.00 ± 1.22	82.75 ± 5.81	75.75 ± 4.73
Epithelial cells	10.75 ± 1.44	8.00 ± 4.74	4.25 ± 2.39
Female			
Polymorphonuclear cells	0.250 ± 0.250	1.000 ± 0.577	16.000 ± 3.606*
Lymphocytes	0.000 ± 0.000	0.000 ± 0.000	1.333 ± 0.882*
Macrophages	84.50 ± 5.52	92.67 ± 0.88	79.00 ± 3.06
Epithelial cells	15.25 ± 5.54	6.33 ± 0.88	3.67 ± 2.33

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
[a] Units are presented as percent of total cells.

TABLE G11
Bronchoalveolar Lavage Fluid Cell Populations of Mice at the 24-Month Interim Evaluation[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
Polymorphonuclear cells	0.200 ± 0.200	13.000 ± 2.345*	16.500 ± 1.803**
Lymphocytes	0.000 ± 0.000	0.375 ± 0.239	0.500 ± 0.289
Macrophages	89.10 ± 2.50	78.25 ± 1.61*	80.33 ± 0.60*
Epithelial cells	10.70 ± 2.61	8.38 ± 1.01	2.67 ± 1.59
Female			
Polymorphonuclear cells	0.000 ± 0.000	7.500 ± 1.607*	20.667 ± 5.918**
Lymphocytes	0.000 ± 0.000	0.500 ± 0.500	0.500 ± 0.500
Macrophages	86.38 ± 3.57	87.00 ± 2.08	73.67 ± 8.46
Epithelial cells	13.63 ± 3.57	5.00 ± 1.00	5.17 ± 3.03

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Units are presented as percent of total cells.

TABLE G12
Phagocytic Activity of Macrophages in Bronchoalveolar Fluid of Mice at the 12-Month Interim Evaluation[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
Phagocytic Activity	85.50 ± 1.44	56.10 ± 2.23*	16.77 ± 2.98**
Female			
Phagocytic Activity	77.07 ± 9.88	52.10 ± 9.22	17.37 ± 6.17**

* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test
** P≤0.01
[a] Units are presented as percent cells phagocytizing sheep erythrocytes.

TABLE G13
Phagocytic Activity of Macrophages in Bronchoalveolar Fluid of Mice at the 18-Month Interim Evaluation[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
Phagocytic Activity	37.43 ± 8.55	14.10 ± 4.54	11.98 ± 2.22*
Female			
Phagocytic Activity	46.85 ± 11.08	20.03 ± 7.45	6.65 ± 0.35*

* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test
[a] Units are presented as percent cells phagocytizing sheep erythrocytes.

Table G14
Viability and Phagocytic Activity of Macrophages in Bronchoalveolar Fluid of Mice at the 24-Month Interim Evaluation

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
Viability[a]	79.20 ± 3.44	64.60 ± 4.15	83.23 ± 0.87
Phagocytic Activity[b]	37.14 ± 9.80	11.90 ± 4.64	3.56 ± 2.25**
Female			
Viability	60.50 ± 8.80	47.17 ± 2.74	59.77 ± 3.21
Phagocytic Activity	21.57 ± 6.77	13.60 ± 4.71	4.35 ± 2.65*

* Significantly different ($P \leq 0.05$) from the control by Dunn's or Shirley's test
** $P \leq 0.01$
a Units are presented as percent viable cells.
b Units are presented as percent cells phagocytizing sheep erythrocytes.

TABLE G15
Measurements of Lung Collagen in Mice at the 6-Month Interim Evaluation

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
Lavage Fluid Collagenous Peptides[a]	67.13 ± 9.76	24.83 ± 8.18	79.64 ± 18.03
Total Lung Collagen[b]	7.42 ± 0.48	7.51 ± 1.38	12.27 ± 4.53
Female			
Lavage Fluid Collagenous Peptides	42.92 ± 8.49	70.83 ± 9.09	51.17 ± 5.14
Total Lung Collagen	4.69 ± 0.35	5.85 ± 0.89	11.00 ± 3.88

[a] Units are presented as μg/g control lung.
[b] Units are presented as mg/g control lung.

TABLE G16
Measurements of Lung Collagen in Mice at the 12-Month Interim Evaluation

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
Lavage Fluid Collagenous Peptides[a]	74.23 ± 9.42	68.73 ± 4.11	117.62 ± 11.87*
Total Lung Collagen[b]	11.94 ± 0.47	12.44 ± 0.82	13.30 ± 1.11
Female			
Lavage Fluid Collagenous Peptides	89.88 ± 12.99	73.66 ± 11.58	108.55 ± 7.56
Total Lung Collagen	11.64 ± 0.48	11.84 ± 0.45	13.78 ± 1.09

* Significantly different ($P \leq 0.05$) from the control by Dunn's or Shirley's test
[a] Units are presented as μg/g control lung.
[b] Units are presented as mg/g control lung.

TABLE G17
Measurements of Lung Collagen in Mice at the 18-Month Interim Evaluation

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
Lavage Fluid Collagenous Peptides[a]	42.54 ± 2.15	51.18 ± 5.40	70.67 ± 8.41**
Total Lung Collagen[b]	6.60 ± 0.49	7.13 ± 0.30	9.70 ± 0.70**
Female			
Lavage Fluid Collagenous Peptides	54.09 ± 11.27	37.68 ± 6.01	64.88 ± 6.56
Total Lung Collagen	6.16 ± 0.25	6.96 ± 0.31	7.34 ± 0.43

** Significantly different ($P \leq 0.01$) from the control by Dunn's or Shirley's test
[a] Units are presented as μg/g control lung.
[b] Units are presented as mg/g control lung.

TABLE G18
Lung Collagen Metabolism and Protein Synthesis in Mice at the 24-Month Interim Evaluation

	0 mg/m^3	6 mg/m^3	18 mg/m^3
Male			
Lavage Fluid Collagenous Peptides[a]	54.39 ± 4.42	65.98 ± 5.01	91.92 ± 4.93**
Total Lung Collagen[b]	8.53 ± 0.71	8.55 ± 0.59	13.71 ± 2.81*
Collagen Production[c]	1.133 ± 0.274	0.779 ± 0.151	1.554 ± 0.291
Non-Collagenous Protein Synthesis[d]	18.73 ± 2.85	16.09 ± 1.15	25.64 ± 2.66
Female			
Lavage Fluid Collagenous Peptides	38.09 ± 4.38	39.26 ± 4.01	62.14 ± 9.04*
Total Lung Collagen	6.04 ± 0.27	6.41 ± 0.36	7.91 ± 0.35*
Collagen Production[c]	1.15 ± 0.33	1.65 ± 0.13	1.33 ± 0.12
Non-Collagenous Protein Synthesis[d]	17.05 ± 2.80	15.45 ± 2.26	27.46 ± 1.57

* Significantly different ($P \leq 0.05$) from the control by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Units are presented as µg/g control lung.
[b] Units are presented as mg/g control lung.
[c] Units are presented as percent new protein.
[d] Units are presented as dpm x 10^{-3}/g control lung.

TABLE G19
Proteinase Activity in Lavage Fluid and Lung Homogenate Supernatant Fluid of Mice at the 6-Month Interim Evaluation[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
Lavage Fluid			
Acid Proteinase	1.27 ± 0.24	1.65 ± 0.47	2.05 ± 0.23
Cathepsin D	0.078 ± 0.038	0.656 ± 0.321*	0.876 ± 0.107*
Cathepsin B	1.006 ± 0.239	0.992 ± 0.716	0.954 ± 0.010
Homogenate Supernatant Fluid			
Acid Proteinase	5.83 ± 1.07	8.10 ± 0.78	7.45 ± 0.64
Cathepsin D	2.27 ± 0.46	3.30 ± 0.57	–[b]
Cathepsin B	3.56 ± 0.80	4.80 ± 0.58	–
Neutral Proteinase	0.634 ± 0.039	0.360 ± 0.043*	–
PMN Elastase Cathepsin G	0.446 ± 0.014	0.418 ± 0.357	–
Macrophage Elastase Collagenase	0.207 ± 0.058	0.340 ± 0.154	–
Female			
Lavage Fluid			
Acid Proteinase	0.762 ± 0.089	1.595 ± 0.038**	1.346 ± 0.097
Cathepsin D	0.457 ± 0.166	0.998 ± 0.016	0.628 ± 0.113
Cathepsin B	0.260 ± 0.068	0.571 ± 0.063	0.718 ± 0.094*
Homogenate Supernatant Fluid			
Acid Proteinase	4.35 ± 0.31	6.95 ± 0.61*	5.77 ± 0.61
Cathepsin D	1.78 ± 0.12	3.89 ± 1.52*	3.12 ± 0.06*
Cathepsin B	2.57 ± 0.22	3.06 ± 1.01	2.65 ± 0.56
Neutral Proteinase	0.522 ± 0.047	0.535 ± 0.039	0.848[c]
PMN Elastase Cathepsin G	0.416 ± 0.033	0.347 ± 0.066	–
Macrophage Elastase Collagenase	0.106 ± 0.043	0.188 ± 0.058	–

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Units are presented as mg/hour/mg control lung.
[b] n=0; no data recorded
[c] n=1; no statistic calculated

TABLE G20
Proteinase Activity in Lavage Fluid and Lung Homogenate Supernatant Fluid of Mice at the 12-Month Interim Evaluation[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
Lavage Fluid			
Acid Proteinase	1.65 ± 0.13	2.11 ± 0.82	3.25 ± 0.28
Cathepsin D	0.403 ± 0.163	0.970 ± 0.244	1.796 ± 0.306**
Cathepsin B	1.25 ± 0.10	1.25 ± 0.78	1.46 ± 0.05
Homogenate Supernatant Fluid			
Acid Proteinase	7.21 ± 0.50	9.35 ± 0.07*	16.50 ± 0.95**
Cathepsin D	5.32 ± 0.27	7.71 ± 0.16*	14.32 ± 1.27**
Cathepsin B	1.89 ± 0.48	1.64 ± 0.10	2.18 ± 0.39
Neutral Proteinase	0.386 ± 0.055	1.029 ± 0.416	1.088 ± 0.271*
PMN Elastase Cathepsin G	0.110 ± 0.110	0.005 ± 0.005	0.209 ± 0.148
Macrophage Elastase Collagenase	0.426 ± 0.159	1.127 ± 0.422	0.879 ± 0.162
Female			
Lavage Fluid			
Acid Proteinase	1.94 ± 0.17	1.79 ± 0.35	3.60 ± 0.33*
Cathepsin D	0.526 ± 0.263	0.463[b]	1.525 ± 0.266*
Cathepsin B	1.50 ± 0.41	2.14[b]	2.08 ± 0.08
Homogenate Supernatant Fluid			
Acid Proteinase	7.88 ± 0.24	10.48 ± 0.50*	16.92 ± 1.84**
Cathepsin D	6.40 ± 0.70	8.44 ± 0.51	14.76 ± 1.59**
Cathepsin B	1.55 ± 0.54	2.04 ± 0.22	2.16 ± 0.55
Neutral Proteinase	0.423 ± 0.183	0.601 ± 0.108	0.824 ± 0.057
PMN Elastase Cathepsin G	0.215 ± 0.125	0.213 ± 0.213	0.190 ± 0.124
Macrophage Elastase Collagenase	0.280 ± 0.116	0.446 ± 0.127	0.653 ± 0.158

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
a Units are presented as mg/hour/mg control lung.
b n=1; no statistic calculated

TABLE G21
Proteinase Activity in Lavage Fluid and Lung Homogenate Supernatant Fluid of Mice at the 18-Month Interim Evaluation[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
Lavage Fluid			
Acid Proteinase	0.264 ± 0.044	0.428 ± 0.120	0.384 ± 0.066
Cathepsin D	0.212 ± 0.046	0.073 ± 0.013*	0.051 ± 0.035*
Cathepsin B	0.069 ± 0.037	0.355 ± 0.127*	0.342 ± 0.057*
Homogenate Supernatant Fluid			
Acid Proteinase	3.29 ± 0.58	4.76 ± 0.49	8.38 ± 0.85**
Cathepsin D	2.71 ± 0.24	4.98 ± 0.63*	8.45 ± 0.63**
Cathepsin B	0.607 ± 0.327	0.053 ± 0.053	0.403 ± 0.270
Neutral Proteinase	0.425 ± 0.079	0.548 ± 0.022	0.528 ± 0.034
PMN Elastase Cathepsin G	0.158 ± 0.066	0.242 ± 0.061	0.254 ± 0.017
Macrophage Elastase Collagenase	0.286 ± 0.093	0.306 ± 0.041	0.275 ± 0.031
Female			
Lavage Fluid			
Acid Proteinase	0.267 ± 0.103	0.561 ± 0.126	0.382 ± 0.040
Cathepsin D	0.219 ± 0.085	0.012 ± 0.012	0.062 ± 0.036
Cathepsin B	0.088 ± 0.034	0.587 ± 0.095*	0.358 ± 0.098*
Homogenate Supernatant Fluid			
Acid Proteinase	3.97 ± 0.41	5.57 ± 0.26*	9.03 ± 0.88**
Cathepsin D	3.28 ± 0.23	5.37 ± 0.16*	9.17 ± 0.75**
Cathepsin B	0.694 ± 0.284	0.232 ± 0.096	0.265 ± 0.265
Neutral Proteinase	0.381 ± 0.041	0.540 ± 0.036*	0.583 ± 0.035*
PMN Elastase Cathepsin G	0.265 ± 0.038	0.391 ± 0.038	0.268 ± 0.041
Macrophage Elastase Collagenase	0.116 ± 0.033	0.149 ± 0.054	0.315 ± 0.045*

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Units are presented as mg/hour/mg control lung.

TABLE G22
Proteinase Activity in Lavage Fluid and Lung Homogenate Supernatant Fluid of Mice at the 24-Month Interim Evaluation[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
Lavage Fluid			
Acid Proteinase	1.62 ± 0.14	1.92 ± 0.18	3.56 ± 0.67*
Cathepsin D	0.000 ± 0.000	0.260 ± 0.156	1.613 ± 0.632**
Cathepsin B	1.94 ± 0.19	1.72 ± 0.28	1.78 ± 0.29
Homogenate Supernatant Fluid			
Acid Proteinase	9.23 ± 1.16	13.85 ± 1.56	24.34 ± 2.66*
Cathepsin D	6.63 ± 0.96	10.82 ± 0.98*	18.75 ± 1.73**
Cathepsin B	2.60 ± 0.39	3.03 ± 0.78	5.58 ± 1.11*
Neutral Proteinase	0.417 ± 0.072	0.568 ± 0.104	0.862 ± 0.164*
PMN Elastase Cathepsin G	0.251 ± 0.034	0.382 ± 0.093	0.341 ± 0.106
Macrophage Elastase Collagenase	0.166 ± 0.063	0.186 ± 0.040	0.521 ± 0.250
Female			
Lavage Fluid			
Acid Proteinase	0.854 ± 0.077	1.012 ± 0.149	0.998 ± 0.212
Cathepsin D	0.194 ± 0.089	0.114 ± 0.114	0.402 ± 0.146
Cathepsin B	0.708 ± 0.118	1.000 ± 0.365	0.596 ± 0.305
Homogenate Supernatant Fluid			
Acid Proteinase	7.83 ± 1.11	9.76 ± 0.56	22.54 ± 1.29*
Cathepsin D	5.10 ± 0.67	8.04 ± 0.95	17.93 ± 0.55**
Cathepsin B	2.73 ± 0.47	1.71 ± 0.57	4.61 ± 1.00
Neutral Proteinase	0.454 ± 0.096	0.646 ± 0.143	0.922 ± 0.077*
PMN Elastase Cathepsin G	0.172 ± 0.063	0.341 ± 0.082	0.360 ± 0.093
Macrophage Elastase Collagenase	0.421 ± 0.293	0.314 ± 0.162	0.563 ± 0.102

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Units are presented as mg/hour/mg control lung.

APPENDIX H
CHEMICAL CHARACTERIZATION, ANALYSIS, AND GENERATION OF CHAMBER CONCENTRATIONS

CHEMICAL CHARACTERIZATION, ANALYSIS, AND GENERATION OF CHAMBER CONCENTRATIONS

PROCUREMENT AND CHARACTERIZATION OF TALC

Talc was obtained from Walsh and Associates (North Kansas City, MO) in two lots (lot W101882 and lot B5415). Lot W101882 was used from the beginning of the 2-year studies through January 1986. Lot B5415 was used in the 2-year studies from 27 January 1986 to the end of the studies on 31 October 1986. The talc was extensively characterized by the analytical chemistry laboratory, Midwest Research Institute (MRI; Kansas City, MO) and McCrone Associates (Norcross, GA). Reports on analyses performed in support of the talc studies are on file at the National Institute of Environmental Health Sciences.

The two lots of the chemical, a finely powdered white solid, were identified as talc by infrared spectroscopy. All spectra were consistent with those expected for the structure and with the literature spectra of talc (*Sadtler Standard Spectra*), as shown in Figure H1.

Lot W101882 was divided into three subbatches, which were analyzed separately. Each subbatch was characterized by elemental analyses, Karl Fischer water analysis, spark source mass spectrometry, and microscopic analyses. Microscopic analysis of each lot consisted of polarized light microscopy (PLM) and transmission electron microscopy (TEM). For PLM the sample was mounted in refractive index liquids and the optical parameters were determined. Dispersion staining has the advantage that small quantities of asbestos can easily be detected since the optical properties are interpreted from bright colors seen on a black background. The colors seen are the results of differences in refractive index dispersion for a liquid and a solid. TEM was performed by sonically dispersing approximately 0.1 g of talc in a solution of 0.001% methyl cellulose in particle-free water. A drop of the suspension was placed on a carbon coated 200-mesh copper grid, and 20 grid openings were examined. The detection limit was 0.1% by weight. No asbestos fibers were detected in any of the subbatches by polarized light microscopy or transmission electron microscopy.

Elemental analyses of hydrogen, magnesium, and silicon for all three subbatches of the lot were in agreement with the theoretical values for talc. The major impurities were 0.7% aluminum and 1.0% iron. Karl Fischer water analysis indicated approximately 0.2% absorbed water. Spark source mass spectrometry for the three subbatches also indicated approximately 0.1% phosphorus, 0.5% fluorine, and 0.05% calcium, while the remaining elemental impurities were less than 0.01%.

A special study was performed on this lot to determine if the sample met the American Society for Testing and Materials standard specifications for magnesium silicate. Results indicated that lot W101882 met the standard specifications.

Automated scanning electron microscopic analysis demonstrated that the talc was virtually free of silica. In the analysis a sample of talc is suspended in methylcellulose. Under computer control the particles are located, and maximum, minimum, and average diameters are determined; then a chemical analysis is performed. Of the 1,466 particles that were examined, 1 was identified as silica, 1,241 were talc, 136 were of tremolite type composition, 77 were mixed silicates, 1 was possibly zircon, and 10 were not identified. The single silica particle had an average diameter of 3.9 μm.

Lot B5415 was characterized by elemental analyses, Karl Fischer water analysis, spark source mass spectrometry, and microscopic analyses using the same methods described for lot W101882. Elemental analyses values were similar to results obtained for lot W101882. The major impurities present were 0.1% calcium, 0.5% aluminum, and 1% iron. Karl Fischer water analysis indicated 1.2% absorbed water. Spark source mass spectrometry also indicated 0.04% phosphorus, >0.5% aluminum, 0.03% sodium, 0.35% fluorine, and all other impurities were less than 0.03%. Microscopic analyses using PLM and TEM detected no asbestos fibers.

Comparative purity analyses of the two lots used in these studies were conducted due to problems with the generation of inhalation concentrations. Four samples of talc were used, two samples each from lots W101882 and B5415. Samples A and B were from lot W101882, sample C was from lot B5415, and sample D was a frozen reference from lot B5415 that had been stored at MRI.

Analyses performed included elemental analyses, microscopic analyses (PLM, TEM, determination of particle size distribution, and aspect ratios), X-ray diffraction, and thermogravimetric analysis (TGA). PLM and TEM analyses were performed on samples C and D. Analysis by PLM followed the procedures described earlier; TEM followed the same procedure described earlier except the talc was sonically dispersed in a solution of 90% (v/v) isopropanol in particle-free water. The determinations of particle size distribution and aspect ratios were performed on all four samples. Using TEM for both analyses, selected area diffraction (SAD) patterns were used to confirm that the particles being measured were talc. The particle size was taken as the average of two diameters 90° to each other and aspect ratios were taken as the ratio of the two diameters. Thermogravimetric analysis (TGA) was performed on samples A, B, and C on a DuPont 910 differential scanning calorimeter (DSC) with calcium oxalate monohydrate used as a calibrating standard, at an initial temperature of 50° C with a programmed maximum temperature of 1,100° C, at a rate of 20° C per minute.

Elemental analyses for hydrogen, magnesium, and silicon for all four samples were in agreement with theoretical values. Polarized light microscopy (PLM) and transmission electron microscopy (TEM) detected no asbestos fibers in any of the samples. The results for particle size distribution and aspect ratios indicated that there were only minor differences in particle size between the samples and more than 75% of the particles were in the 1.0 to 3.0 µm range. More than 90% of the talc particles had aspect ratios between 1 and 1.4, and less than 1% had ratios greater than 3:1. X-ray diffraction confirmed that all four samples were primarily talc with small quantities of chlorite and dolomite. Thermogravimetric analysis indicated that samples A, B, and C were similar. A main peak at 912° C in all three samples caused by the loss of chemically combined water was equal to a loss of 4.7% by weight. A minor peak at 590° C in all three samples may represent the loss of CO_2 from dolomite and amounted to a loss of 0.7% by weight which is equivalent to 1.5% dolomite.

Size Distribution Analysis of Talc Samples (% of Total Particles Counted)

Size Range (µm)	Talc A	Talc B	Talc C	Talc D
0.5–1.0	5.88	2.97	12.50	1.94
1.0–1.5	15.69	9.90	19.23	11.65
1.5–2.0	26.47	26.73	24.04	26.21
2.0–2.5	20.59	17.82	21.15	23.30
2.5–3.0	11.76	18.81	10.58	8.74
3.0–3.5	5.88	12.87	4.81	7.77
3.5–4.0	3.92	5.94	2.88	5.83
4.0–4.5	2.94	1.98	1.92	4.85
4.5–5.0	2.94	0.99	0.96	3.88
5.0–5.5	1.96	0.99	0.96	2.91
5.5–6.0	1.96	0.99	0.96	1.94
6.0–6.5	-	-	-	0.97

The moisture content of the bulk chemical was reanalyzed every 4 months at the study laboratory by determining the weight loss following heating at 120°C for 16 hours. The results indicated that the moisture content of the talc was similar between the two lots and did not change during the 2-year studies. Bulk chemical stability studies were not performed on talc because the physical and chemical properties of talc indicate that it should be stable over a wide range of temperatures. The compound was stored in tightly sealed plastic bags at 25° C.

Generation and Monitoring of Chamber Concentrations

Aerosol Generation System: Talc aerosol was generated from one 4-inch, fluid bed generator (FBG). Figure H2 shows the schematic of the FBG with the gravity feed and collecting pan collection systems. The FBG bed contained type 316 stainless steel powder (Hoeganaes Corporation, Riverton, NJ), consisting of irregularly shaped particles 125 to 180 μm in diameter. The stainless steel powder was cleaned prior to use. The cleaning system used a 4-inch FBG with dry, filtered air flowing through at a flow rate of 80 CFM. The high flow rate through the bed removed the finest stainless steel particles. The cleaning system was run for 24 hours to ensure that all the "fines" were removed.

Following cleaning of the bed material, talc was mixed with the stainless steel powder at approximately 1 to 2.5 g of talc per 500 g bed material. The concentration of talc in the bed material was one method used to adjust exposure concentrations in the chamber. During the time period of November 1985 to January 1986, when difficulty in maintaining target concentrations was experienced, higher loadings were used in an effort to maintain target concentrations.

For generation of the talc aerosol, fluidization of the bed material mixed with talc occurred when compressed air ($\approx$200 Lpm) was injected into the bed through a porous metal distribution plate which supports the bed. The motion of the bed released the much smaller talc particles into the air; the larger, heavier stainless steel particles were retained in the bed. A Kr-85 discharger was placed above the bed to reduce the particle charges. The aerosolized talc particles were mixed with diluting air ($\approx$200 Lpm) to achieve the desired concentrations and were then delivered to the exposure chambers (Figures H3 and H4). As the talc powder was removed from the bed, the bed material was continually drained from the FBG through an overflow port located at the side of the generator. As spent bed material was drained from the generator, fresh talc-containing bed material was constantly added into the generator from a hopper located above the generator.

Stainless steel multitiered whole-body exposure chambers (H2000, Lab Products, Inc.) were used to expose the rats in this study while the smaller H1000 chambers were used for the mice. Flow rates through the chambers were 12 ± 2 CFM. To reduce the spatial variation of aerosol concentration and to increase the uniformity of mixing, the aerosol was diluted using a dilutor prior to its introduction into the chamber. Also, animal cages were rotated once per week to reduce the variation of concentrations of talc aerosols that the rodents were exposed to during the 2-year studies.

Aerosol Concentration Monitoring: Aerosol concentrations in each exposure chamber were monitored by taking filter samples for three, 2-hour periods during each 6-hour exposure day. The background concentration of total suspended particles in each control chamber was monitored each exposure day by taking one 6-hour filter sample. Overnight filter samples for total suspended particles were taken from the 18 mg/m^3 chambers once per month. All filter samples were taken at a flow rate of 3 L/minute. Each filter was weighed before and after the sample was taken, and the aerosol mass concentrations were calculated by dividing the mass increment (mg) by the volume sampled (m^3); the means and standard deviations for each chamber were calculated for each exposure day. Weekly mean exposure concentrations for the 2-year studies are presented in Figures H5 through H8. The concentrations during non-exposure hours in the 18 mg/m^3 chambers ranged from 0.02 to 1.1 mg/m^3.

A RAM-S continuous aerosol monitor was used to monitor the stability of the aerosol concentrations and to determine the need to adjust the aerosol generation system during exposures. The RAM-S was used to monitor each chamber for at least 5 minutes at the beginning, middle, and end of the filter sampling period. A 2 L/minute flow rate through the RAM-S was achieved using an internal pump in the device. Both RAM-S and filter samples were taken at one point of the chambers above the animal cage. A Y-shaped probe was used, allowing simultaneous filter sampling and RAM-S aerosol mass monitor operation. The overall temporal variation in chamber concentrations in the 2-year studies were 33% and 27% relative standard deviation (RSD) for the mouse 6 and 18 mg/m^3 chambers. The variations were 31% and 36% RSD for the rat 6 and 18 mg/m^3 chambers. At least a portion of this variability may be ascribed to the period when talc generation problems were encountered (November 1985 through February 1986). In addition, a portion of the variability for the 18 mg/m^3 rat chamber

may be ascribed to the time when higher concentrations were being generated (September through November, 1984).

During the period of November 5, 1985 through January 27, 1986 difficulties were experienced maintaining the required exposure levels of talc for the lifetime and 2-year exposure studies. Concentrations of aerosolized talc were significantly below target. Attempts were made to increase the flow of talc into the generator and raise the concentration; however, the talc-laden stainless steel bed material fed into the generator less freely than it had prior to November, 1985. There were no observable chemical changes in either the talc or the stainless steel bed material and no malfunctions in the generation system which could be pinpointed as the underlying cause for the poor flow characteristics of the bed material. On January 27, 1986, the generator was restarted with a new batch of talc. After a stabilization period of three weeks, the flow properties of the bed material showed significant improvement.

It was also observed during February, 1986 that when the ratio of talc to bed material was increased above 1.6 g talc per 500 g bed material, the bed began to show the poor flow properties characteristic of the previous batch of talc. When the bed loading was reduced below 1.6 g talc per 500 g bed material, the flow properties stabilized. This indicated that the bed has a maximum loading limit which must not be exceeded. By March 1986, the generator had stabilized and chamber target concentrations were achieved. The exact cause of these generation problems was never resolved.

In November, 1984 it was noticed that the RAM-S monitor indicated an off-scale reading (>10 V which is equivalent to 20 mg/m^3) for the 18 mg/m^3 rat chamber. Reasonable agreement was seen between RAM-S readings and filter samples in the other chambers. Investigations of this discrepancy indicated that the airflow through the critical orifice controlling flow through the filter was reduced. Evaluation of the previously collected pressure drop associated with this orifice and one having nearly identical nominal flow revealed that the flow to the sampling filter of the high level rat chamber dropped significantly on September 24, 1984. These data suggest that the sampling orifice had become partially clogged. In order to obtain a correction factor to recalculate the chamber concentration data, the filter pressure drop and exposure chamber pressure drop data were retrieved and used to determine the actual pressure drop across the sampling filter for the time period of September 24 through November 14, 1984. A group of 18 filters from different lots of the type used to sample the talc exposure chambers were tested to determine the pressure drop across them as a function of the flow through the filter. These data indicated that values for flow could be calculated from the pressure drop data. The relationship between pressure drop and filter flow rate was used to recalculate the sampling filter flow for each day. When the chamber sampling orifice flow rate was taken into account, the best estimate of the correction factor is 2.06. This factor has been used to multiply the originally recorded chamber concentrations for those dates. The corrected values are reported.

Aerosol size distribution was determined once a month for each chamber using a cascade impactor operated at a flow rate of 15 L/minute. Stainless steel disks coated with apiezon grease were used as impactor substrates and the amount of talc collected on each stage was determined by the difference in stage weight before and after the sample was taken. The mass medium aerodynamic diameter and the geometric standard deviation were calculated from the mass data, effective cutoff diameter of each stage, and impactor flow rate. The results are presented in Tables H1 and H2.

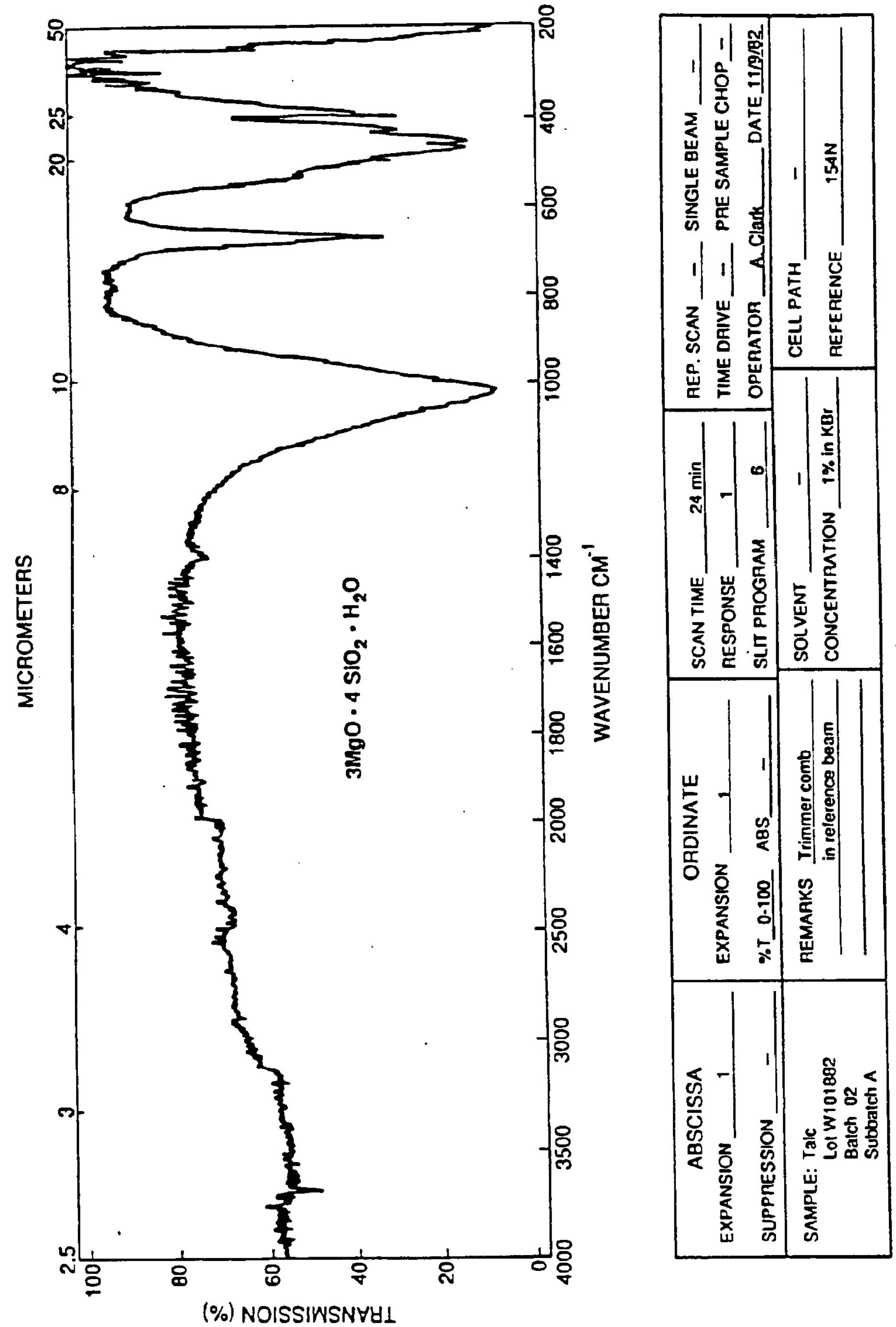

FIGURE H1
Infrared Absorption Spectrum of Talc

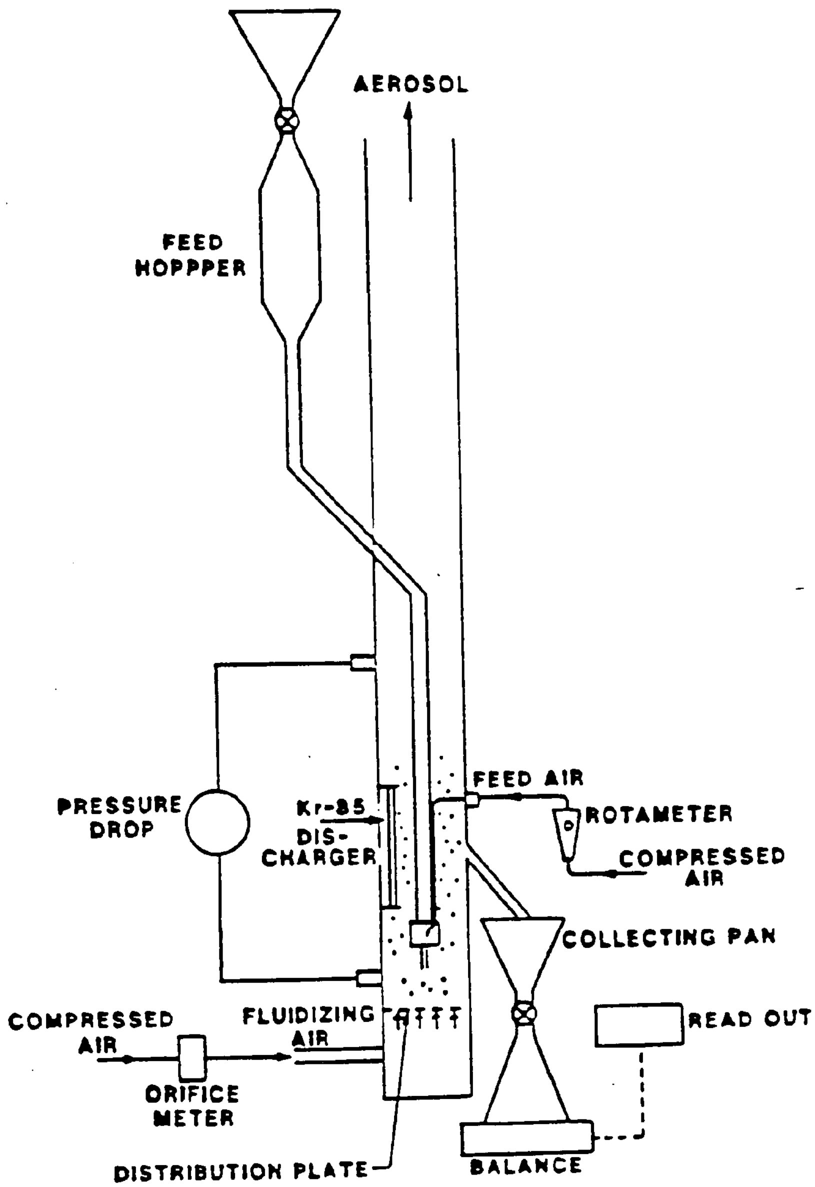

FIGURE H2
Fluid Bed Generator

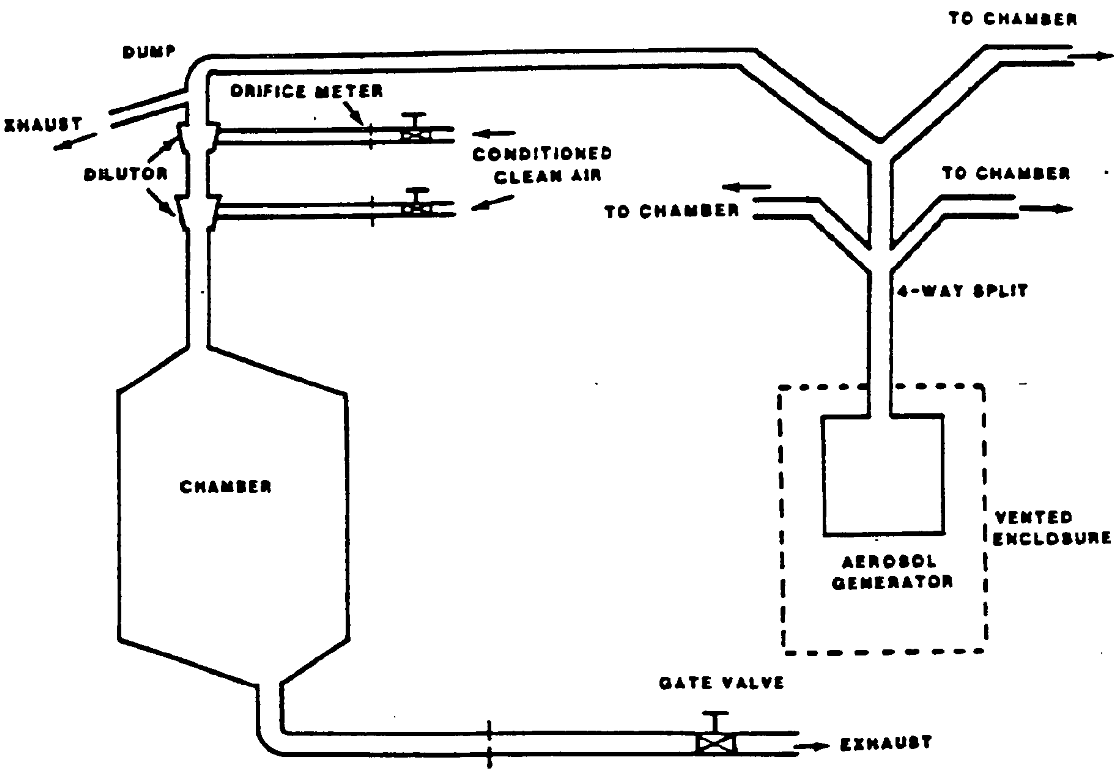

FIGURE H3
Aerosol Dilution/Delivery System

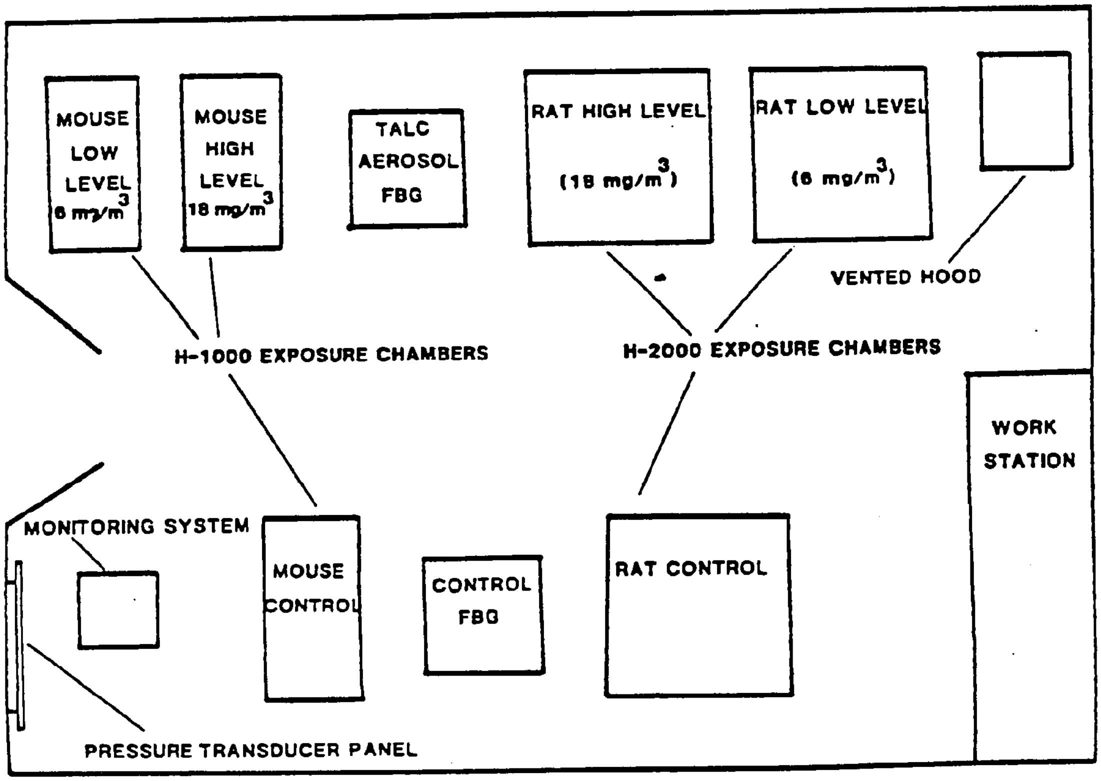

FIGURE H4
Talc Chronic Exposure System

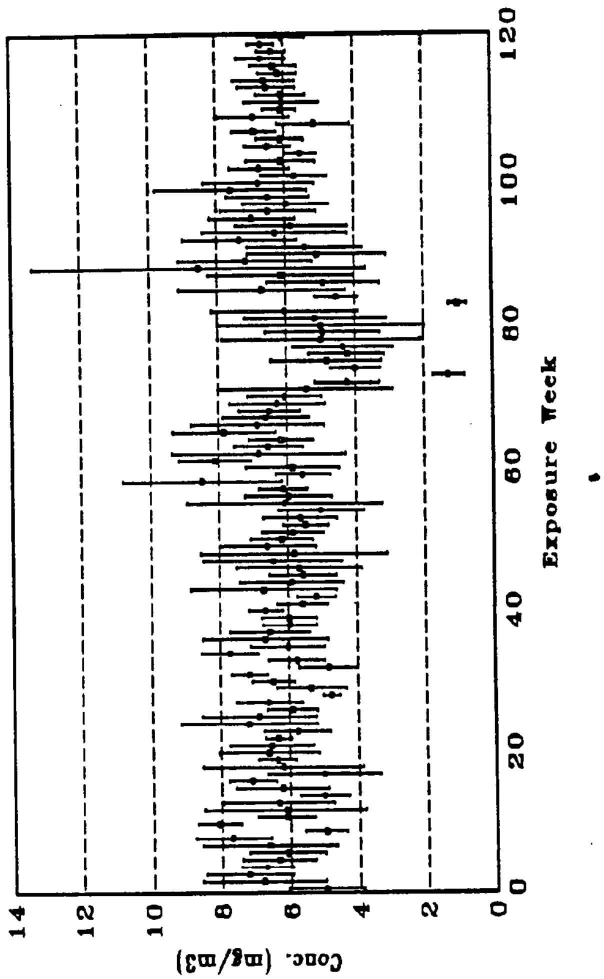

FIGURE H5
Talc Aerosol Filter Concentrations in the 6 mg/m³ Rat Chamber

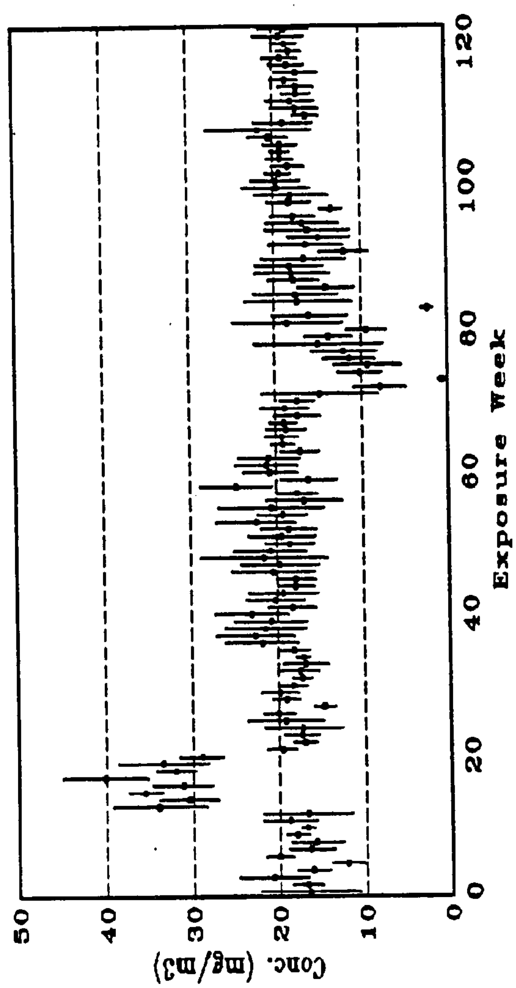

FIGURE H6
Talc Aerosol Filter Concentrations in the 18 mg/m^3 Rat Chamber

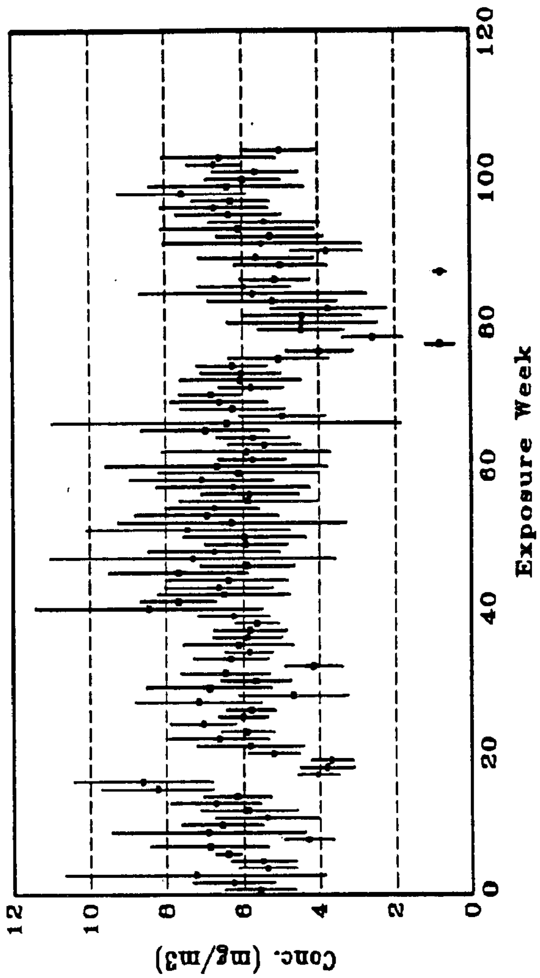

FIGURE H7
Talc Aerosol Filter Concentrations in the 6 mg/m³ Mice Chamber

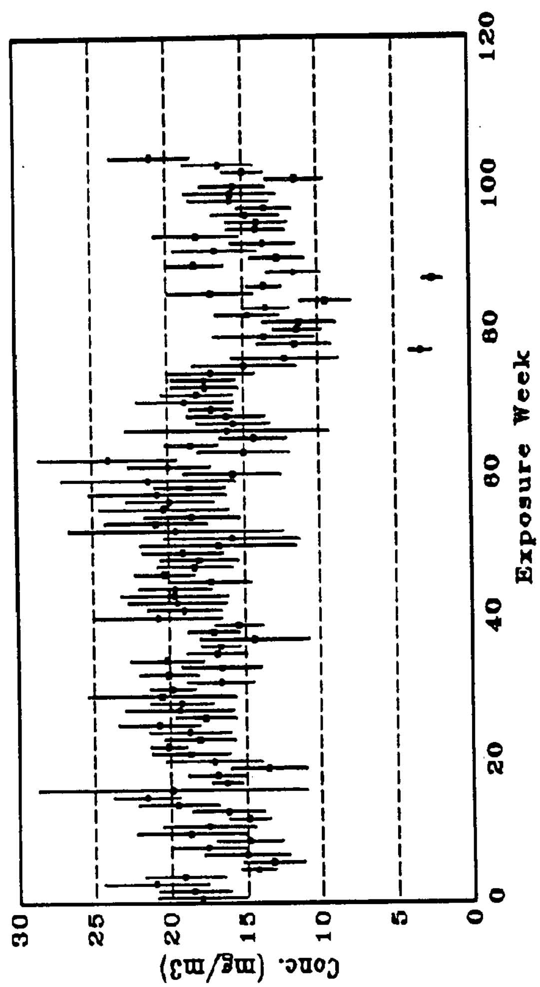

FIGURE H8
Talc Aerosol Filter Concentrations in the 18 mg/m³ Mice Chamber

TABLE H1
Summary of Aerosol Size Measurements for the 6 and 18 mg/m³ Rat Chambers

6 mg/m³			18 mg/m³		
Date	Mass Median Aerodynamic Diameter (µm)	Geometric Standard Deviation	Date	Mass Median Aerodynamic Diameter (µm)	Geometric Standard Deviation
9 July 1984	2.3	2.6	25 June 1984	3.6	2.0
6 August 1984	2.6	1.7	1 August 1984	3.0	1.8
4 September	2.8	1.8	27 August 1984	3.2	1.9
3 October 1984	2.6	1.8	26 September 1984	2.9	1.8
31 October 1984	2.9	1.8	24 October 1984	3.2	1.9
27 November 1984	2.5	1.8	20 November 1984	3.0	1.9
4 January 1985	2.6	1.8	24 December 1984	2.8	1.8
25 January 1985	2.5	1.7	14 January 1985	2.9	1.8
25 February 1985	2.6	1.8	19 February 1985	2.8	1.8
19 March 1985	2.8	1.8	15 March 1985	3.1	2.0
22 April 1985	2.9	1.7	12 April 1985	3.1	1.8
13 June 1985	3.0	1.9	8 May 1985	2.9	1.9
9 July 1985	2.8	1.8	10 June 1985	3.0	1.9
9 August 1985	2.7	1.9	5 July 1985	3.5	1.8
3 September 1985	2.7	1.5	1 August 1985	3.1	1.9
30 September 1985	2.3	1.3	26 August 1985	2.9	1.9
28 October 1985	2.6	1.4	23 September 1985	2.6	1.6
2 December 1985	3.1	1.7	21 October 1985	2.7	1.5
18 December 1985	3.0	1.7	25 November 1985	4.0	2.1
3 January 1986	1.8	2.8	17 December 1985	3.3	1.9
8 January 1986	3.6	1.9	30 December 1985	3.7	1.8
13 January 1986	3.1	1.8	3 January 1986	4.0	2.2
24 February 1986	2.9	2.2	8 January 1986	3.8	1.9
24 March 1986	3.4	1.9	18 February 1986	3.2	2.1
22 April 1986	3.2	2.3	17 March 1986	3.6	1.9
23 May 1986	2.4	1.9	14 April 1986	4.0	2.0
23 May 1986	2.9	1.9	19 May 1986	3.2	1.8
27 May 1986	2.3	1.9	2 June 1986	3.2	2.1
16 June 1986	2.7	2.7	17 June 1986	3.3	1.9
30 June 1986	2.2	2.4	15 July 1986	3.4	2.0
28 July 1986	2.5	2.3	11 August 1986	3.1	1.9
25 August 1986	2.1	2.5	9 September 1986	2.9	1.9
22 September 1986	2.5	2.0	6 October 1986	2.7	2.3
20 October 1986	2.7	2.3			
Mean ± standard deviation	2.7 ± 0.4	1.9 ± 0.4		3.2 ± 0.4	1.9 ± 0.2

TABLE H2
Summary of Aerosol Size Measurements for the 6 and 18 mg/m³ Mouse Chambers

6 mg/m³			18 mg/m³		
Date	Mass Median Aerodynamic Diameter (µm)	Geometric Standard Deviation	Date	Mass Median Aerodynamic Diameter (µm)	Geometric Standard Deviation
18 June 1984	3.9	1.8	25 June 1984	3.6	2.0
16 July 1984	3.4	1.9	23 July 1984	3.7	1.9
14 August 1984	3.5	1.8	20 August 1984	3.5	1.8
18 September 1984	3.3	1.8	10 September 1984	3.9	2.0
10 October 1984	3.1	1.9	17 October 1984	3.8	1.9
7 November 1984	3.3	1.8	19 November 1984	3.5	1.7
4 December 1984	3.0	1.8	12 December 1984	3.3	1.9
7 January 1985	3.4	1.6	7 January 1985	3.4	1.8
4 February 1985	3.2	1.8	8 February 1985	3.6	1.9
1 March 1985	2.9	1.9	7 March 1985	3.6	1.9
29 March 1985	3.1	1.8	5 April 1985	3.5	1.9
23 April 1985	3.6	1.8	2 May 1985	3.6	1.8
22 May 1985	3.1	2.0	29 May 1985	3.5	2.2
21 June 1985	3.3	1.8	26 June 1985	3.7	2.0
23 July 1985	3.4	1.8	29 July 1985	3.5	1.9
15 August 1985	3.5	1.8	20 August 1985	3.8	1.9
9 September 1985	2.6	1.3	16 September 1985	3.3	1.8
7 October 1985	2.7	1.5	14 October 1985	2.8	1.7
4 November 1985	2.5	1.5	12 November 1985	4.1	2.1
9 December 1985	3.4	1.6	16 December 1985	3.8	2.0
19 December 1985	3.6	2.0	3 January 1986	3.6	1.9
3 January 1985	3.9	2.0	8 January 1986	5.0	2.0
8 January 1986	4.0	2.1	10 February 1986	3.3	2.4
20 January 1986	3.7	1.8	13 March 1986	3.1	2.5
3 March 1986	3.0	2.1	7 April 1986	3.4	2.0
31 March 1986	2.9	2.1	5 May 1986	3.3	2.2
28 April 1986	3.2	4.7			
Mean ± standard deviation	3.3 ± 0.4	1.9 ± 0.6		3.6 ± 0.4	2.0 ± 0.2

APPENDIX I
INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH-07 RAT AND MOUSE RATION

TABLE I1
Ingredients of NIH-07 Rat and Mouse Ration[a]

Ingredients[b]	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Dried brewer's yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

[a] NCI, 1976; NIH, 1978
[b] Ingredients were ground to pass through a U.S. Standard Screen No. 16 before being mixed.

TABLE I2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]

	Amount	Source
Vitamins		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D_3	4,600,000 IU	D-activated animal sterol
K_3	2.8 g	Menadione
d-α-Tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	*d*-Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B_{12}	4,000 μg	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	*d*-Biotin
Minerals		
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

[a] Per ton (2,000 lb) of finished product

TABLE I3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.22 ± 0.72	21.1–23.5	13
Crude fat (% by weight)	5.59 ± 0.55	4.7–6.4	13
Crude fiber (% by weight)	3.36 ± 0.30	2.7–3.8	13
Ash (% by weight)	6.55 ± 0.23	6.1–7.0	13
Amino Acids (% of total diet)			
Arginine	1.308 ± 0.606	1.210–1.390	8
Cystine	0.306 ± 0.084	0.181–0.400	8
Glycine	1.150 ± 0.047	1.060–1.210	8
Histidine	0.576 ± 0.024	0.531–0.607	8
Isoleucine	0.917 ± 0.029	0.881–0.944	8
Leucine	1.946 ± 0.055	1.850–2.040	8
Lysine	1.270 ± 0.058	1.200–1.370	8
Methionine	0.448 ± 0.128	0.306–0.699	8
Phenylalinine	0.987 ± 0.140	0.665–1.110	8
Threonine	0.877 ± 0.042	0.824–0.940	8
Tryptophane	0.236 ± 0.176	0.107–0.671	8
Tyrosine	0.676 ± 0.105	0.564–0.794	8
Valine	1.103 ± 0.040	1.050–1.170	8
Essential Fatty Acids (% of total diet)			
Linoleic	2.393 ± 0.258	1.830–2.570	7
Linolenic	0.280 ± 0.040	0.210–0.320	7
Vitamins			
Vitamin A (IU/kg)	9,846 ± 2,839	5,600–15,000	13
Vitamin D (IU/kg)	4,450 ± 1,382	3,000–6,300	4
α-Tocopherol (ppm)	37.95 ± 9.41	22.5–48.9	8
Thiamine (ppm)	20.77 ± 2.01	17.0–23.0	13
Riboflavin (ppm)	7.92 ± 0.87	6.10–9.00	8
Niacin (ppm)	103.4 ± 26.59	65.0–150.0	8
Pantothenic acid (ppm)	29.54 ± 3.60	23.0–34.0	8
Pyridoxine (ppm)	9.55 ± 3.48	5.60–14.0	8
Folic acid (ppm)	2.25 ± 0.73	1.80–3.70	8
Biotin (ppm)	0.254 ± 0.042	0.19–0.32	8
Vitamin B_{12} (ppb)	38.45 ± 22.01	10.6–65.0	8
Choline (ppm)	3,089 ± 328.69	2,400–3,430	8
Minerals			
Calcium (%)	1.17 ± 0.09	1.06–1.41	13
Phosphorus (%)	0.92 ± 0.03	0.87–0.99	13
Potassium (%)	0.883 ± 0.078	0.772–0.971	6
Chloride (%)	0.526 ± 0.092	0.380–0.635	8
Sodium (%)	0.313 ± 0.390	0.258–0.371	8
Magnesium (%)	0.168 ± 0.010	0.151–0.181	8
Sulfur (%)	0.280 ± 0.064	0.208–0.420	8
Iron (ppm)	360.5 ± 100	255.0–523.0	8
Manganese (ppm)	92.0 ± 6.01	81.70–99.40	8
Zinc (ppm)	54.72 ± 5.67	46.10–64.50	8
Copper (ppm)	11.06 ± 2.50	8.090–15.39	8
Iodine (ppm)	3.37 ± 0.92	1.52–4.13	6
Chromium (ppm)	1.79 ± 0.36	1.04–2.09	8
Cobalt (ppm)	0.681 ± 0.14	0.490–0.780	4

TABLE I4
Contaminant Levels in NIH-07 Rat and Mouse Ration

	Mean ± Standard Deviation[a]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.72 ± 0.19	0.33–0.94	13
Cadmium (ppm)	<0.1		13
Lead (ppm)	0.57 ± 0.31	0.14–1.32	13
Mercury (ppm)	<0.05		13
Selenium (ppm)	0.35 ± 0.08	0.21–0.44	13
Aflatoxins (ppb)	<5.0		13
Nitrate nitrogen (ppm)[b]	12.56 ± 4.47	2.80–18.0	13
Nitrite nitrogen (ppm)[b]	0.14 ± 0.11	<0.10–0.50	13
BHA (ppm)[c]	2.54 ± 1.05	<2.00–5.00	13
BHT (ppm)[c]	2.39 ± 1.33	<1.00–4.00	13
Aerobic plate count (CFU/g)[d]	39,523 ± 39,878	3,400–130,000	13
Coliform (MPN/g)[e]	3.72 ± 1.79	<3.00–9.00	11
Coliform (MPN/g)[f]	9.46 ± 14.11	<3.00–43.0	13
E. coli (MPN/g)[g]	3.08 ± 0.28	<3.0–4.00	13
Total nitrosamines (ppb)[h]	6.99 ± 4.13	1.80–16.00	13
N-Nitrosodimethylamine (ppb)[h]	5.67 ± 3.79	0.80–15.00	13
N-Nitrosopyrrolidine (ppb)[h]	1.32 ± 0.73	1.00–3.40	13
Pesticides (ppm)			
α-BHC[i]	<0.01		13
β-BHC	<0.02		13
γ-BHC	<0.01		13
δ-BHC	<0.01		13
Heptachlor	<0.01		13
Aldrin	<0.01		13
Heptachlor epoxide	<0.01		13
DDE	<0.01		13
DDD	<0.01		13
DDT	<0.01		13
HCB	<0.01		13
Mirex	<0.01		13
Methoxychlor	<0.05		13
Dieldrin	<0.01		13
Endrin	<0.01		13
Telodrin	<0.01		13
Chlordane	<0.05		13
Toxaphene	<0.1		13
Estimated PCBs	<0.2		13
Ronnel	<0.01		13
Ethion	<0.02		13
Trithion	<0.05		13
Diazinon	<0.1		13
Methyl parathion	<0.02		13
Ethyl parathion	<0.02		13
Malathion[j]	0.09 ± 0.07	0.05–0.28	13
Endosulfan I	<0.01		13
Endosulfan II	<0.01		13
Endosulfan sulfate	<0.03		13

TABLE I4
Contaminant Levels in NIH-07 Rat and Mouse Ration (continued)

[a] For values less than the limit of detection, the detection limit is given for the mean.
[b] Sources of contamination: alfalfa, grains, and fish meal
[c] Sources of contamination: soy oil and fish meal
[d] CFU = colony forming unit
[e] MPN = most probable number
[f] Includes two high values of 39 and 43 MPN/g obtained from lots milled 15 March 1984 and 9 May 1984, respectively.
[g] One lot milled 17 October 1984 contained 4.00 MPN/g; all other lots contained 3.00 MPN/g
[h] All values were corrected for percent recovery.
[i] BHC = hexachlorocyclohexane or benzene hexachloride.
[j] Seven lots contained more than 0.05 ppm.

APPENDIX J
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via serology on sera from extra (sentinel) animals in the study rooms. These animals and the study animals are subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Rats

Prior to the beginning of the lifetime study, 5 F344/N rats of each sex were sacrificed and serum samples were taken for serological evaluation by Microbiological Associates (Bethesda, MD). Serum samples were also taken from selected rats for serology testing at each of the interim evaluations: 3 male and 3 female rats at 6 months; 8 male and 9 female rats at 12 and 18 months; 11 male and 17 female rats at 24 months; and 15 male and 15 female rats at the terminal sacrifice (male, 113 weeks; female, 122 weeks). Blood collected from each animal was allowed to clot and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates (Bethesda, MD) for determination of antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
ELISA	
RCV/SDA (rat corona virus/sialodacryoadenitis virus)	Study initiation, 6, 12, 18, 24 months, study termination
PVM (pneumonia virus of mice)	6, 12, 18, 24 months, study termination
Sendai	6, 12, 18, 24 months, study termination
Mycoplasma arthritidis	12, 18, 24 months, study termination
Mycoplasma pulmonis	12, 18, 24 months, study termination
CARB (cilia-associated respiratory bacillus)	Study termination (males only)
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	Study initiation, 6, 12, 18, 24 months, study termination
KRV (Kilham rat virus)	Study initiation, 6, 12, 18, 24, study termination
PVM	Study initiation
Sendai	Study initiation
Immunofluorescence Assay	
KRV	24 months (males only)
RCV (rat corona virus)	24 months (males only)
RCV/SDA	28 months (males only)

Mice

Prior to the beginning of the 2-year study, 5 $B6C3F_1$ mice of each sex were sacrificed and serum samples were taken for serological evaluation by Microbiological Associates (Bethesda, MD). Serum samples for serology testing were also taken from control males and females at each of the interim evaluations (4 males and 4 females at 6 months; 12 males and 12 females at 12 months) and at the terminal sacrifice (15 males and 15 females). (Samples were inadvertently omitted for mice evaluated after 18 months of exposure on 4-5 December, 1985.) Blood collected from each animal was allowed to clot and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates (Bethesda, MD) for determination of antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
Complement Fixation	
LCM (lymphocytic choriomeningitis virus)	Study initiation, 6, 12, 24 months
Mouse adenoma virus	Study initiation
ELISA	
Ectromelia virus	6, 12, 24 months
GDVII (mouse encephalomyelitis virus)	Study initiation, 6, 12, 24 months
MHV (mouse hepatitis virus)	Study initiation, 6, 12, 24 months
PVM	6, 12, 24 months
Sendai	6, 12, 24 months
Reo 3	6, 12, 24 months
Mouse adenoma virus	6, 12, 24 months
M. arthritidis	6, 12, 24 months
M. pulmonis	6, 12, 24 months
Hemagglutination Inhibition	
Ectromelia virus	Study initiation
K (papovirus)	12, 24 months
MVM (minute virus mice)	Study initiation, 6, 12, 24 months
PVM	Study initiation
Polyoma virus	Study initiation, 6, 12, 24 months
Reovirus 3	Study intitiation
Sendai	Study initiation
Immunofluorescence Assay	
EDIM (Epizootic diarrhea of infant mice)	6, 12, 24 months
Reovirus 3	24 months

TABLE J1
Murine Virus Antibody Determinations for Rats and Mice in the Lifetime and 2-Year Inhalation Studies of Talc

	Interval (months)	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
Rats			
	6 months	0/6	-
	12 months	0/17	-
	18 months	0/17	-
	24 months		
	(males)	1/11	KRV
		9/11	Sendai
		6/11	RCV
	(females)	13/17	Sendai
		13/17	RCV/SDA
	28 months		
		15/15	Sendai
		3/15	RCV/SDA
	30 months	15/15	Sendai
		1/15	RCV/SDA
Mice			
	6 months	0/8	-
	12 months	0/24	MHV
	24 months	2/30	Reovirus 3
		7/30	*M. arthritidis*
		21/30	EDIM

APPENDIX K
4-WEEK INHALATION STUDIES IN RATS AND MICE

EXPERIMENTAL PROTOCOL

Procurement and Characterization of Talc

Talc was obtained from Walsh and Associates (North Kansas City, MO) in one lot (lot number W101882). Identity and purity analyses were performed by the analytical chemistry laboratory, Midwest Research Institute (MRI; Kansas City, MO).

The study chemical, a finely powdered white solid, was identified as talc by infrared spectroscopy, elemental analysis, and microscopic analyses. The moisture content of the bulk chemical was analyzed and was determined to be stable throughout the studies. Bulk chemical studies were not conducted due to the physical and chemical properties of talc. The compound was stored in sealed Nalgene containers.

Generation and Monitoring of Chamber Concentrations

Talc aerosols were generated in a fluidized bed generator by injecting filtered air into the bed. Samples were collected continuously during the 6-hour exposure day on glass fiber filters. Only one sampling port position was used each day to collect the samples from each chamber. Once a week, samples were collected on Zefluor filters so that the magnesium content of aerosolized talc could be determined and be compared to the magnesium content of bulk talc. Cascade impactor samples were taken 3 to 6 times a week to determine aerosol particle size. The amount of talc collected on the filters and impactor stages was quantitated gravimetrically. The extent of carry over of the stainless steel material from the FBG was quantitated by measuring the amount of acid soluble nickel and chromium in filter samples taken from the exposure atmosphere twice during the study.

Study Design

Groups of 10 male and 10 female F344/N rats and B6C3F$_1$ mice were exposed by inhalation to talc at target concentrations of 0 (chamber controls), 2, 6, and 18 mg/m^3. Rats and mice were exposed for 6 hours daily, 5 days a week, for 20 days.

Source and Specification of Animals

Male and female F344/N rats were obtained from Lovelace Inhalation Toxicology Research Institute (Albuquerque, NM). Male and female B6C3F$_1$ mice were obtained from Simonsen Laboratory (Gilroy, CA). Rats and mice were held 3 weeks before the studies began, and were 6 to 7 weeks old when the studies began. Animal health was monitored by serologic analyses during the studies under the protocols of the NTP Sentinel Animal Program.

Animal Maintenance

Rats and mice were housed individually throughout the studies. Drinking water was available *ad libitum*. Further details of animal maintenance are given in Table K1.

Clinical Examinations and Pathology

All rats and mice were observed twice daily. Clinical observations and body weights were recorded at the beginning of the studies, each week, and at the end of the studies. Organ weights were recorded for the heart, right kidney, liver, and lung at the end of the studies.

A necropsy was performed on all animals. During necropsy, all organs and tissues were examined for grossly visible lesions. A complete histopathologic examination was performed on all high-exposure and control animals. Tissues for microscopic examination were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned to a thickness of 5 μm, and stained with hematoxylin and eosin.

TABLE K1
Experimental Design and Materials and Methods in the 4-Week Inhalation Studies of Talc

Study Laboratory
Lovelace Inhalation Toxicology Research Institute (Albuquerque, NM)

Strain and Species
Rats: F344/N rats
Mice: B6C3F$_1$ mice

Animal Source
Rats: Lovelace Inhalation Toxicology Research Institute (Albuquerque, NM)
Mice: Simonsen Laboratory (Gilroy, CA)

Time Held Before Studies
3 weeks

Average Age When Placed on Studies
6-7 weeks

Date of First Exposure
Rats: 20 April 1983
Mice: 16 June 1983

Duration of Exposure
6 hours/day, 5 days/week for 4 weeks

Date of Last Exposure
Rats: 18 May 1983
Mice: 13 July 1983

Average Age When Killed
10 to 11 weeks

Method of Sacrifice
Intraperitoneal injection of T-61 solution

Necropsy Dates
Rats: 19-20 May 1983
Mice: 14-15 July 1983

Size of Study Groups
10 males and 10 females

Method of Animal Distribution
Randomized by weight

Animals per Cage
1

Method of Animal Identification
Ear tag and toeclip

Diet
NIH-07 Rat and Mouse Ration (Zeigler, Bros., Gardner, PA) available *ad libitum* during non-exposure periods

Maximum Storage Time for Feed
Not available

Water
Automatic Watering System (Edstrom Industries, Waterford, WI), available *ad libitum*

Cages
Stainless steel mesh cages (Hazleton, Aberdeen, MD), changed once weekly

TABLE K1
Experimental Design and Materials and Methods in the 4-Week Inhalation Studies of Talc (continued)

Chambers
Stainless steel multitiered whole-body exposure chambers (H2000 and H1000, Hazleton Systems, Aberdeen, MD) washed once weekly

Excreta Pan
Techboard untreated paper (Shepherd Specialties Paper, Inc., Kalamazoo, MI), changed twice a day

Filters
Room Air and Chamber Air High Efficiency Particulate Air (HEPA) Filter, MIL Spec MIL-F-51068C (Flanders, Washington, DC), changed as required

Animal Room Environment

Rats
Average temperature: 23° C
Relative humidity: 40.3%
Fluorescent light: not available
Room air changes: not available

Mice
Average temperature: 24° C
Relative humidity: 42%
Fluorescent light: not available
Room air changes: not available

Exposure Concentrations
0, 2, 6, and 18 mg/m^3 by inhalation

Type and Frequency of Observation
Observed twice daily; body weights and clinical findings recorded at study initiation and weekly thereafter

Necropsy
Necropsy was performed on all animals.

Histopathology
Complete histopathologic examinations performed on all high-exposure and control animals. In addition to tissue masses, gross lesions, and associated lymph nodes, tissues examined included: larynx, lung, nasal turbinates, trachea, and tracheobronchial lymph nodes.

RESULTS

Rats

All rats survived to the end of the study and there were no clinical findings related to talc exposure. The mean body weights and final mean body weights of exposed male and female rats were similar to those of the controls.

There were no significant increases in any organ-weight-to-body-weight ratios in male or female rats. The talc lung burdens increased with talc exposure level; however, the ratio of lung burden to exposure concentration was somewhat higher at the 6 and 18 mg/m^3 exposure levels. The increase in talc lung burden to exposure concentration may be because the maximum ability of the respiratory tract to clear particles was exceeded at the 6 and 18 mg/m^3 exposure levels.

There was a minimal increase in the number of intra-alveolar macrophages in the lung of male and female rats exposed to 18 mg/m^3. The lesion was diffuse in nature and in no instance were clusters of greater than three alveolar macrophages observed. The individual macrophages were slightly larger than normal and had cytoplasm which contained fine eosinophilic granules.

Mice

One male mouse exposed to 2 mg/m^3 and one male mouse exposed to 6 mg/m^3 died before the end of the study. The survival of exposed male and female mice was similar to that of the controls. The mean weights and final mean body weights of exposed male and female mice were similar to those of the controls. There were no clinical findings associated with exposure to talc aerosols.

There were no significant changes in any organ-weight-to-body-weight ratios in exposed male or female mice. Talc lung burdens increased with talc exposure level. However, the ratio of lung burden to exposure concentration was constant at all exposure levels. In contrast to rats, the maximum ability of the respiratory tract to clear particles was apparently not exceeded at the 18 mg/m^3 level.

The only lesions related to inhalation of talc aerosols were observed in the lung of male and female mice exposed to 18 mg/m^3. However, the changes were minimal and consisted of a diffuse increase in the number of intra-alveolar macrophages. In most cases, pulmonary macrophages did not exceed two per alveolus, but occasional clusters of up to 10 alveolar macrophages were observed. The individual macrophages were two to three times normal size with foamy granular cytoplasm.

EXHIBIT 14

C·T·F·A

Representing the personal care products industry

E. Edward Kavanaugh
President

Plaintiff's Exhibit No. P-14

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DRAFT MINUTES

TALC INTERESTED PARTY TASK FORCE

CTFA
Main Conference Room
1101 17th Street, N.W., Suite 300
Washington, DC 20036

July 21, 1993

A meeting of the Talc Interested Party Task Force was held at CTFA on Wednesday, July 21, 1993 beginning at 10:00 a.m. Those in attendance were:

Dr. Laureen MacEachern - **COLGATE-PALMOLIVE**
Ms. Kate Trammell - **MAYBELLINE**
Mr. William Ashton - **JOHNSON & JOHNSON (Guest)**
Mr. Mike Chudkowski - **JOHNSON & JOHNSON**
Mr. Richard Zazenski - **LUZENAC AMERICA**
Dr. Martin Roddy - **NOXELL**
Ms. Marjorie McTernan - **JOHNSON & JOHNSON (Guest)**
Dr. Stephen Gettings - **CTFA (Liaison)**

I. OPENING REMARKS

1. SGettings opened the meeting and apologized for calling it at such short notice. He noted that the purpose of the meeting was to discuss the outcome of a meeting SGettings held with members of the Planning Committee of the International Society of Regulatory Toxicology & Pharmacology (ISRTP), held at the ToxForum meeting on July 14th, 1993. The minutes of the last meeting were approved with no changes.

II. INFORMATION EXCHANGE/GENERAL DISCUSSION

1. SGettings noted that ISTRP have been asked by FDA to organize a 1-2 day symposium on talc safety and related issues (93-TA-10). The Task Force was alerted as to this possibility in February, 1993 (93-TA-07).

2. At the ISRTP Planning Committee meeting SGettings was

apprised of the following:

The intended target audience are regulatory specialists, toxicologists, food/drug/cosmetic/medical device manufacturers, academicians and medical professionals. At least 100 attendees are anticipated.

From the meeting, FDA hope to gain insight into the relevance of recent toxicological and epidemiological studies to the safety of regulated products. FDA would like participants to address not only the validity of experimental approach but also risk "under conditions of use." FDA does not anticipate that they will be able to develop a regulatory decision from this program alone.

The meeting will be held in the Washington, DC area, possibly at the NIH auditorium. It will be scheduled for late fall (probably November) or for early 1994 (January).

The symposium will relate principally to ingredient use and safety as it applies to consumer products. (FDA anticipate that scientific studies relating to occupational uses of talc will contribute to the program as it relates to consumer products). Relative to OTC drug use of talc, FDA feel that someone from USP should at least serve on the panel for discussion and possibly make a presentation on USP specifications. Apparently, the OTC group thinks there should be a discussion of product labeling as it applies to OTC products, i.e., diaper rash could be discussed for adequacy and possible suggestions. FDA feel that this portion of the program would be useful in assessing whether or not the current USP specifications are adequate.

The proceedings of the symposium will probably be published (probably as a meeting summary, by rapporteurs).

FDA is budgeting $10,000 as financial contribution to the effort; industry has been asked to contribute $20,000; the remainder will be provided by ISRTP.

The anticipated format is to have some sort of "expert panel" in attendance throughout the meeting. FDA suggest that someone from industry (possibly a member of the CIR Expert Panel) and a consumer representative be invited to sit on the panel. Following the presentations, FDA would like to have ample time for discussions from the floor. The discussion will be led by members of the panel.

3. The following agenda has been proposed following discussions between ISRTP and FDA:

DAY 1 - The first day of the symposium will concentrate on inhalation health considerations, and will take the following format:

Introduction - introduce the topic, present the reasons for holding the symposium and provide some background about studies conducted on the safety of talc (historical perspective). ISRTP have been asked to identify someone who can serve in this capacity.

Manufacture of talc - To discuss (1) how, and where, it is obtained (mineral sources), (2) specifications for talc as used in different products, and (3) quality control including steps to control and monitor asbestos contamination. FDA stress that it is important for this presentation to describe the "specifications" for the material that is actually used in different products (i.e., particle size, impurities, etc). CTFA has been asked to identify a suitable speaker.

Uses of talc in different FDA-regulated products - Specifically, what are the requirements for the use of talc in foods, drugs, cosmetics and medical devices and why they are critical. (FDA suggest that this presentation may be combined with the previous one).

Regulatory status of talc in the different product categories - This topic will be discussed by one (or more) FDA officials.

Health Perspectives - Presentation and critique of the NTP inhalation study by various presenters (eg., Oberdorster, Goodman etc).

Panel/Floor discussion

DAY 2 - The second day will primarily cover ovarian cancer and talc, but epidermatology as it relates to inhalation exposure with will also be discussed.

Introduction - historical overview of the various epidemiology studies on talc (possibly in 2 parts):

a. Epidemiology studies of occupational exposures (inhalation).

b. Epidemiology studies on ovarian cancer.

Risk factors in ovarian cancer

Harlow's Epidemiology studies of ovarian cancer and perineal exposure.

Meta-Analysis - Discussion of the pros and cons of meta-analysis as a general statistical tool in measuring correlations in epidemiology studies.

Panel/Floor discussion

Moderator wrap-up and close

III. ACTION/NEXT STEPS

1. The Task Force agreed that it was clear that the ISTRP meeting will be held irrespective of industry input, but that such input was important. The Task Force agreed that it was important that, as industry's representative, SGettings continue to participate at the ISRTP Planning Committee meetings and to offer advice and suggestions as outlined by the Task Force.

2. The Task Force agreed that the level of sponsorship requested by industry was not prohibitive. CTFA will send out commitment forms requesting total sponsorship from the Task Force of $20,000 (depending upon the number of participants, as low as $1,000 per company).

3. The Task Force agreed that Dr. Bruce Semple (formerly of J&J, now with P&G) should be approached and asked to represent industry on the Panel (both days of the meeting).

4. The Task Force agreed that a representative of one of the talc suppliers should make a presentation on (1) the production, processing and quality control of talc manufacturer; and (2) particle size and specifications for different product applications. RZazenski agreed to provide a presentation outline and a suggested speaker within the next few days. The Task Force agreed that all speakers will be representing the industry and that the Task Force will approve the contact of each industry presentation.

5. The Task Force agreed that a representative of a finished-product manufacturers should make a presentation on consumer use/risk assessment of cosmetic products containing talc. SGettings will get clarification on whether other speakers will address similar issues as they relate to other talc uses. The Task Force suggested that BSemple would again be the most appropriate industry representative. The Task Force agreed to begin assembling data which might form the basis of such a presentation. It was noted that some of this information (on particle size and product notices) had previously been requested by FDA and that the Task Force had not been successful in collecting such information.. WAshton

agreed to review, in particular, J&J's published data on exposure to talc. RZazenski noted that a lot of useful information could be derived from the report prepared by JKalse for the Task Force. LMacEachern noted the presentation should reference recent studies on talc (93-TA-12). LMacEachern noted that the presentation should emphasize the safety of talc use.

6. The Task Force agreed to review available information on occupational exposure from inhalation, and to discuss this issue at a follow-up meeting.

7. The Task Force agreed that both Dr. Oberdorster and Dr. Wehner (both co-authors of the BEC Report) should be proposed as speakers (on lung overload mechanisms and the biological implausibility of ovarian cancer from talc exposure, respectively). The Task Force agreed that industry should arrange for their attendance (at cost), ever if they are not selected as speakers. It was also suggested that the Task Force may wish to arrange for the attendance of other consultants if necessary.

IV. ADJOURNMENT/NEXT MEETING

1. It was noted that SGettings next meets with ISRTP in early August. The Task Force agreed to hold a follow-up conference call within the next few days and to arrange a Task Force meeting in early September.

2. There being no further business, the meeting was adjourned.

Respectfully submitted,

IARC - inadequate evidence to show carcinogenicity

Formulate Question/answers regarding anything on TALC

Stephen D. Gettings, Ph.D., D.A.B.T.
CTFA

— literature survey ~ publications —

ISRP - INDUSTRY FRIENDLY

Exposure data into presentation - Consumer use

Specific questions from panel or audience, need experts to address questions.

Langer - IARC comm, Brooklyn Coll.

— JWKs for search

— Press response [illegible] —

— Mark Ross (Geological Survey)

Silica - issue cosmetic Talc (B.P) that contain crystalline silica that (0.1%) that is a carcinogen, Industrial use - labeling req't if > 0.1% silica carcinogen

EXHIBIT 15

CTFA

THE COSMETIC, TOILETRY, AND FRAGRANCE ASSOCIATION

MEMORANDUM

E. EDWARD KAVANAUGH
PRESIDENT

DATE: February 13, 1998

TO: **TALC INTERESTED PARTY TASK FORCE**

FROM: Pandora Dennis
Administrative Assistant - Science

Please deliver this and the following page(s) to the corresponding individual in your company. Thank you.

Ms. Debra Ambrose/**POLAR MINERALS/(812) 838-4744**
Mr. William Ashton/**JOHNSON & JOHNSON/(908) 874-1254**
Ms. Donna Beach/**COSMAIR/(908) 499-2929**
Dr. Daniel Briggs/**PROCTER & GAMBLE/(513) 626-4399**
Mr. Michael Chudkowski/**JOHNSON & JOHNSON/(908) 874-1254**
Mr. Shawn Hays/**POLAR MINTERALS/(404) 934-4376**
Dr. John Hopkins/**JOHNSON & JOHNSON/(908) 874-1155**
Mr. Daniel Johnson/**COMBE INCORPORATED/(914) 694-1585**
Mr. John Kelse/**RT VANDERBILT COMPANY/(203) 853-1452**
Mr. Louis Kotyuk/**WHITTAKER, CLARK & DANIELS/(800) 833-8139**
Mr. Mike Larson/**MINERALS TECHNOLOGIES/(212) 878-1804**
Dr. Laurie Pan/**MARY KAY COSMETICS/(214) 905-6799**
Dr. Steve Pennisi/**COMBE INCORPORATED/(914) 694-1585**
Mr. Thomas Pallone/**ALBERTO-CULVER/(708) 450-3067**
Dr. Thomas Re/**BRISTOL-MYERS/(908) 851-6250**
Ms. Janice Rogers/**GILLETTE/(301) 590-1535**
Dr. Bruce Semple/**PROCTER & GAMBLE/ (513) 626-2977**
Dr. Tracey Spriggs/**COLGATE-PALMOLIVE/ (908) 878-7844**
Ms. Elaine Stern/**HELENE CURTIS/(312) 384-3539**
Ms. Joan Thomas/**CTPA/(011) 441714938061**
Dr. Maureen Toulon/**AVON/(914) 369-2898**
Mr. Richard Zazenski/**LUZENAC AMERICA/(303) 643-0446**

H:\SCIENCE\LJL\DATA\WPDOCS\TALC\FAXCOVER.2

1101 17TH ST., N.W., SUITE 300 WASHINGTON, D.C. 20036-4702
202.331.1770 FAX 202.331.1969
http://www.ctfa.org
SECURING THE INDUSTRY'S FUTURE SINCE 1894

Plaintiff's Exhibit No. P-83

EXHIBIT 16

Plaintiff's Exhibit No. P-13

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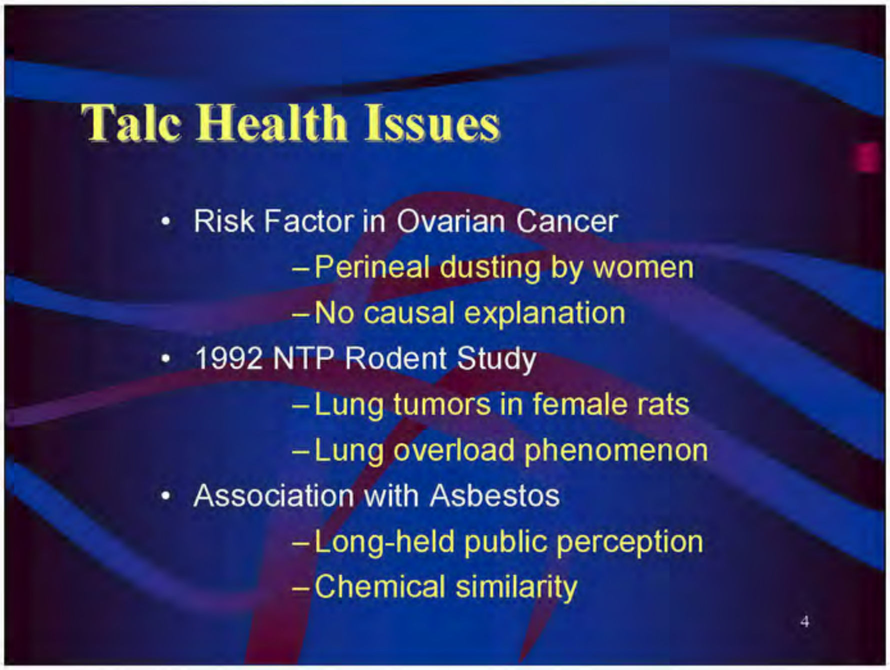
–1

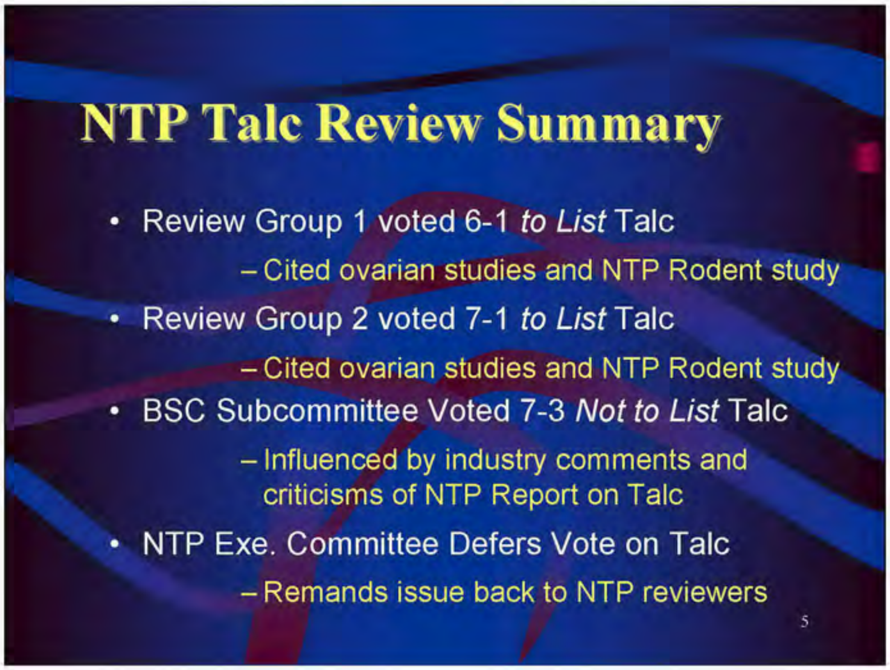

Regulatory Issue
National Toxicology Program (NTP)
– Coordinates Interagency Toxicological Testing
– Publishes Report on Carcinogens (RoC)
– Minimal Threshold for Carcinogenic Listing
– Listing Triggers OSHA and Prop 65 Labeling
– Conducted Talc Inhalation Study on Rodents
– Nominated Talc for Review in 2000
2

NTP Listing Consequences

- Immediate Loss of Personal Care Market
  - $10,000,000 in Year 1
- Deterioration of all Markets due to Labeling
  - 20 to 50% of remaining sales year 3
- Regulated as a Carcinogen Worldwide
- Talc Litigation likely to Proliferate

3


Talc Health Issues
• Risk Factor in Ovarian Cancer
– Perineal dusting by women
– No causal explanation
• 1992 NTP Rodent Study
– Lung tumors in female rats
– Lung overload phenomenon
• Association with Asbestos
– Long-held public perception
– Chemical similarity
4


NTP Talc Review Summary
• Review Group 1 voted 6-1 *to List* Talc
– Cited ovarian studies and NTP Rodent study
• Review Group 2 voted 7-1 *to List* Talc
– Cited ovarian studies and NTP Rodent study
• BSC Subcommittee Voted 7-3 *Not to List* Talc
– Influenced by industry comments and criticisms of NTP Report on Talc
• NTP Exe. Committee Defers Vote on Talc
– Remands issue back to NTP reviewers
5


Luzenac Defense Strategies
• Unite Behind the Cosmetic, Toiletry & Fragrance Association (CTFA)
• Engage Services of the "Center for Regulatory Effectiveness (CRE)"
• Aggressive Corporate Position
6

–6

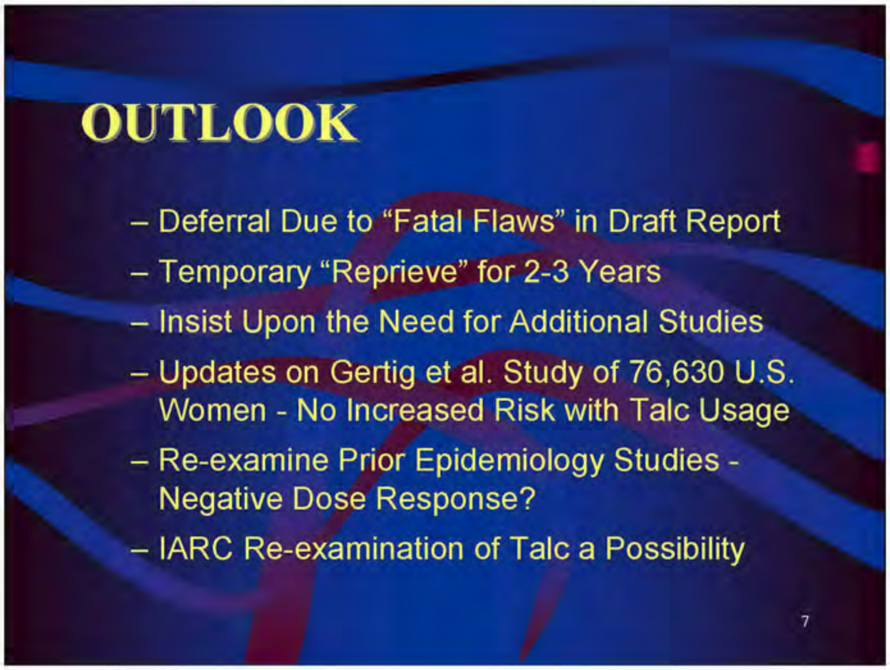

OUTLOOK
– Deferral Due to "Fatal Flaws" in Draft Report
– Temporary "Reprieve" for 2-3 Years
– Insist Upon the Need for Additional Studies
– Updates on Gertig et al. Study of 76,630 U.S. Women - No Increased Risk with Talc Usage
– Re-examine Prior Epidemiology Studies - Negative Dose Response?
– IARC Re-examination of Talc a Possibility
7

EXHIBIT 17

C·T·F·A

Representing the personal care products industry

92-SE-328

92-SAC-24

E. Edward Kavanaugh
President

MEMORANDUM

TO: Scientific Advisory Committee

FROM: G.N. McEwen, Jr., Ph.D., J.D.
Vice President - Science

DATE: July 17, 1992

SUBJ: TALC SAFETY INTERESTED PARTY

The conclusions in two recent studies question the safety of cosmetic grade talc. A draft report of one study, involving daily, lifetime inhalation of massive amounts of talc in rats and mice, concludes there is clear evidence that talc is a carcinogen for female rats, and some evidence that it is a carcinogen for male rats. There was no evidence of carcinogenicity in male or female mice. The other study concludes that there is an association between talc use in the perineal area and ovarian cancer in women. CTFA will provide copies of these reports upon request.

Although CTFA is convinced that these studies do not suggest any hazard from normal use or foreseeable misuse of personal-care products or cosmetics containing talc, such reports may have wide implications for classification and characterization of talc by various regulatory agencies, including OSHA, FDA, and California's Office of Environmental Health Hazard Assessment, responsible for listing substances for Proposition 65.

CTFA has instituted an Interested Party Task Force to address these studies. The Task Force is developing a strategy to defend the continued safe use of talc, and is open to those companies willing to provide financial support for this activity. For further information on how to join the Task Force, please contact Dr. Stephen Gettings, Director, Toxicology, CTFA.

GNM/pcl
cc: Scientific Advisory
Executive Committee

The Cosmetic, Toiletry, and Fragrance Association
1101 17th Street, N.W. • Suite 300 • Washington, D.C. 20036 • (202) 331-1770 • Fax (202) 331-1969

Plaintiff's Exhibit No. P-122

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EXHIBIT 18

CALL REPORT
Luzenac America

Date: 11/8/93
Date of Call: 11/8/93

Regional Manager: J. A. Tracy
Accompanied By:

Cust Name: Carter Wallace
City & State: Trenton, NJ
Contacts: Deborah Richardson, Purchasing Agent

Cust#: 05258/0000
Industry Code: 05:001

Prod#: 11234 Descrip: Vertal 1500USP Qty: 200TPY Price:

Comp#1: DeGussa Prod: Hydrated silica Qty: Price:
Comp#2: Prod: Qty: Price:

PRODUCT APPLICATION: Dusting of latex rubber condoms.

OBJECTIVE: Find out the status of the replacement of talc, and discuss the Johnson plant closing.

SUMMARY: Debbie said that they have switched from talc to hydrated silica that they get from DeGussa. Huber is another approved supplier. She said that the silica is so light and fluffy that they have built a closed dusting system to contain the dust. I asked her if they were not concerned about the use of silica. She said they were, but felt that the only problem was with respirable silica. Their closed system they feel is sufficient protection for their workers.

She said that they were pleased with the performance of talc, but were concerned because a CTFA report in July 1992 said that there was suspicion that talc could cause ovarian cancer. Although the report didn't say that it was a cause, Carter Wallace is concerned about future litigation.

Debbie said that if silica becomes a problem, they might look at talc again.

ACTION REQUIRED: No action required.

Plaintiff's Exhibit No.
P-66
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EXHIBIT 19

January 2, 2002

Principal Argument for Adopting Luzenac America's NTP Strategy

We engaged the council of the Center for Regulatory Effectiveness ("CRE") in November 2000 for the purpose of providing us direct assistance in developing a business strategy to challenge the NTP talc review. CRE 'knows' NTP. CRE knows many of the individuals personally – most importantly, the key decision-makers. They know how NTP operates, both technically and politically. CRE knows how NTP 'values' the significance of published human and animal studies CRE knows the influential people from the other agencies who get involved in the review process. Simply put, CRE possesses the knowledge and experience to help us effectively mount a strategic challenge to the NTP talc review.

From the beginning, CRE has recommended that we adopt an aggressive (professional) approach with NTP. Our technical (and legal) arguments have alternated between Luzenac and CRE letterhead - designed to maximize the intended effect.

Presently, CRE believes the request for by Dr. Olden (NTP Director) presents us with an opportunity to 'proactively' submit a detailed literature research paper that not only directly addresses the unresolved issues (mineralogy), but also other controversial issues that we anticipate will (or should) resurface (epidemiology, causation, consistency of results). It affords us the opportunity to initiate the agenda for discussions with NTP.

To reject their recommendations in this important process would be unwise.

For the Record

In November 2000, Luzenac discovered the "fatal flaw" in the NTP report. With the help of CRE we exploited this issue with NTP which ended in the deferral decision by the NTP Executive Committee.

The public record will reflect that Luzenac America was the only talc-interested-party who recognized this fatal flaw (and winning strategy).

> Meli to NTP; Nov. 30, 2000
> "A critical error in the fundamental logic of the NTP's own line of argument categorically invalidates the NTP conclusion....proposed by RG1 and RG2 that "Talc not containing asbestiform fibers is reasonably anticipated to be a human carcinogen."
>
> 'It is also recommended that the Board of Scientific Counselors Subcommittee notify Review Groups 1 & 2 that their conclusion relative to talc not containing asbestos fibers is not supported by the data. The arguments and assumptions made by the reviewers in the text of the Draft Background Document unquestionably contradict their own conclusion..."
>
> "It is clear that the premise on which NTP has assessed the literature and safety issues relating to all forms of talc is seriously faulted and cannot be used as a reasonable basis for nomination as an anticipated human carcinogen."
>
> Harris to NTP; May 1, 2001
> "..and if they (RG1 and RG2 recommendations) were to be submitted to the Director of NTP and the Secretary as valid recommendations, a final decision to list talc not containing asbestiform fibers in the Report would be arbitrary and capricious, an abuse of discretion, or otherwise not in accordance with law, and would be set aside by the Federal courts pursuant to the Administrative Procedure Act."

Plaintiff's Exhibit No. P-90 exhibitsticker.com

KEY POINTS

1. Joachim Roeser must understand that it was the strategy and actions of Luzenac America (not Luzenac Group or Eurotalc) that led to the talc deferral decision (in order for him to respect our current recommendations). Inexplicably, despite the soundness of our strategy, Luzenac Group repeated opposed our intended actions throughout the process.

2. CTFA and the talc interested parties have been minimally effective during this NTP review. It is a management problem. They have not demonstrated the leadership necessary to coordinate a diligent, on-going defense of talc. In the spirit of "Either lead, follow, or get out of the way", I recommend Luzenac America (with "CRE") advance our agenda with an invitation to others to follow. I do not favor the "committee approach" to NTP where no one is formally in charge.

3. I am not at all concerned about angering CTFA or any of its members who might be customers. With our entire business literally at stake, we have the "standing" to do what we feel is necessary in this battle for survival. As an aside, only J&J and possibly one other company expressed interest in further funding of the consultants utilized by CTFA last December.

4. We have every right to employ scientific reasoning and logic to the evaluation of health studies involving talc (outside of mineralogy issues). If we bring to light questionable conclusions or flaws in a published study, other experts can then be asked to forward their opinions on the issues. At a minimum, the NTP reviewers would be obligated to discuss and debate our points of contention (e.g., talc detected in ovarian tissue).

EXHIBIT 20

Redacted

Redacted

Redacted

Page 2: [1] Deleted	Judy Brown	7/18/2006 10:54:00 AM

July 12, 2006

Mark Ellis
President
Industrial Minerals Association – North America
Suite 301
2011 Pennsylvania Ave. N.W.
Washington, D.C. 20006

Dear Mr. Ellis:

For the benefit of "talc interested parties" in IMA-NA and IMA-Europe, I would like to summarize a few key points as to the reasoning behind Luzenac's decision to forego any further funding of the University of Vermont talc study (re: "Mossman" study) at this time.

1. This study proposal was first brought to Luzenac's attention in early 2005 primarily due to the diligent efforts of Bob Glenn. Luzenac has engaged the consulting services of Bob (through Crowell & Moring) for several years now. Luzenac was prepared to proceed with the study primarily because there was an excellent chance that the study could be completed and a paper written that could be made available for the IARC review in February 2006. We felt that the injection of new data into the talc/ovarian cancer debate was essential. As the months passed and other "talc interested parties" became part of the sponsorship base, numerous and frustrating delays resulted in the postponement of the start of this research project. It became evident in late 2005 that we squandered away the window of opportunity to have this study completed in time for the IARC review meetingpassed

Page 2: [2] Deleted	Judy Brown	7/18/2006 10:54:00 AM

. When IARC concluded their review and classified "perineal use of talc-based powders" as a Group 2b carcinogen, we began to question the value of proceeding any further with the Mossman study. To put it in the vernacular, the "horse has already left the barn." Due to the considerable costs involved and deadlines no longer a factor, Luzenac (Rio Tinto Minerals) made the business decision that the potential value of this study was greatly diminished and did not warrant any further pursuit at this time.

2. The cosmetic and pharmaceutical companies engaged in the business of marketing dusting and body powders to the public have show no enthusiasm for sponsoring new research on this issue.

Page 2: [3] Deleted	Judy Brown	7/18/2006 10:54:00 AM

One of their primary arguments is that there are simply too many positive epidemiology studies published to stem the tide of negative sentiment

Page 2: [4] Deleted	Judy Brown	7/18/2006 10:54:00 AM

additional expenditures for new research in this field if the cosmetic and pharmaceutical companies engaged in this business are reluctant to do so.

3. Over the last nine months Luzenac has been transformed into a new company, Rio Tinto Minerals. As a result, we are undergoing major changes in our product portfolios and business strategies. Our limited R&D resources will be applied to those products which are essential to our stability and growth. Supplying talc for the body powder market is a rather insignificant element in our overall product portfolio and does not warrant any further sponsorship for research projects to support the business.

Sincerely,

Eric Turner

Sincerely,

Eric Turner

Employee Name
Employee Title Line One
Employee Title Line Two

EXHIBIT 21

'97-09-18 00:34 A.P. P.1

ALFRED P. WEHNER, D.M.D., Sc.D., CAND. MED.
DIPLOMATE, ACADEMY OF TOXICOLOGICAL SCIENCES
312 SAINT STREET
RICHLAND, WASHINGTON 99352

9/17/97

Mr.Michael R.Chudkowski
Manager, Preclinical Toxicology
J&J Consumer Products,Inc.
Skillman, NJ 08558-9418

Dear Mike:

There is a German saying which translates as follows:

> "A true friend is not he who beguiles you with flattery but he who discloses to you your mistakes before your enemies discover them."

In this spirit I would like to volunteer a critique of the three CTFA response statements which you faxed me on September 11. Some of the wording leaves CTFA wide open to counter-attack. The most harmless response statement of the three is the one dated July 1,1992. It does not give the names of the authors and the title of the paper to which the response is being made. More important, I believe that different and/or additional more powerful statements along the lines of my critique faxed to Jerry McEwen, as far as applicable to the situation in 1992, would have put CTFA in a more advantageous tactical position. Several investigators have independently reported talc particles in ovarian tissue. Simply citing the Battelle study and stating that it "demonstrated that talc does not <u>translate</u> (sic!) through the cervix to the uterine cavity and beyond" does not address the problem, does not refute these findings, and therefore does not serve CTFA's best interest. All in all, in my opinion an inept response.

The problem with the response statement dated July 8,1992, is more serious. The last sentence in the second paragraph states: "Finally, human studies on talc and cancer in industrial settings have shown that industrial exposure to talc, both by skin contact and inhalation, even at levels thousands of times higher than lifetime consumer exposure, presents no significant risk." This statement is outright false. All an Epstein, a Kennedy, or one of their aides knowledgeable in matters talc, would have to do at a hearing (or any occasion, at that) to demolish the credibility of the talc industry is to refer to the studies by Kleinfeld et al, Thomas, and Thomas and Stewart!

Referring in a 1992 statement to a 1977 editorial in defense of one's position is not a very persuasive argument. Much can happen in 15 years.

509/375-0873 FAX 509/375-5693

Plaintiff's Exhibit No. P-20

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J&J-0115053

Here, too, I believe that more powerful and better defendable arguments could and should have been made on behalf of the industry.

The response statement dated November 17, 1994, is just as bad. The second sentence in the third paragraph reads: "The workshop concluded that, although some of these studies suggested a weak association might exist, when taken together the results of the studies are insufficient to demonstrate any real association." This statement is also inaccurate, to phrase it euphemistically. At that time there had been about 9 studies (more by now) published in the open literature that did show a statistically significant association between hygienic talc use and ovarian cancer. Anybody who denies this risks that the talc industry will be perceived by the public like it perceives the cigarette industry: denying the obvious in the face of all evidence to the contrary. This would be a particularly tragic misperception in view of the fact that the industry does have powerful, valid arguments to support its position.

The workshop did not conclude that "the results of the studies are insufficient to demonstrate any real association." As pointed out above, a "real" statistically significant association has been undeniably established independently by several investigators, which without doubt will be readily attested to by a number of reputable scientists/clinicians, including Bernard Harlow, Debra Novotny, Candace Sue Kasper, Debra Heller, and others. What the workshop panel did conclude was that (1) the results of the studies were ambiguous, inconsistent, contradictory and therefore inconclusive, (2) therefore hygienic use of cosmetic talc does not present a risk to the consumer. So why not use these powerful and irrefutable arguments (plus some of those along the lines of my fax to Rich) instead of questionable mush that leaves one vulnerable to counterattack? The following sentence states: "In addition there is no basis to conclude that talc is capable of migrating to the ovaries...". I submit that several reports, independently describing talc particles in/on ovarian tissue, along with other suggestive evidence (questionable as some of it might be) does provide a basis for just such a conclusion. My point is that such a complex and vexing issue cannot be credibly dismissed with one sweeping statement without any documenting references.

Mike, I realize that CTFA is not J&J. However, I believe that a defeat or embarrassment of CTFA also negatively affects J&J to some extent. As a consultant on a retainer I feel obligated to proactively act in the best interest of my client at all times, not only when I am approached with a specific assignment. This consideration alone motivated me to spend the time to bring my thoughts on this matter to your attention. I trust that in the process I did not step on anybody's toes.

Best regards

Al

J&J-0115054

EXHIBIT 22

NARRATIVE
TALC – NTP REGULATORY CHALLENGE

Good morning everyone. My name is Steve Jarvis and I am responsible for Health, Safety, and Environmental matters for Luzenac America.

This morning…it is my distinct pleasure to present to you a summary of our most recent regulatory challenge involving the National Toxicology Program and their review of talc for potential listing in the 10th Report on Carcinogens.

But first….for those who may not know exactly what we do …..I'd like to introduce you to Luzenac America.

SLIDE 1

Luzenac America is part of the Luzenac Group of Companies. Headquartered in France, Luzenac Group is the world largest commercial producer of talc products.

In North America…….. Luzenac America operates 4 talc mines and 8 talc milling operations…….We have large operations based in Ontario, Vermont, and Montana. ………… Luzenac America is

1

Plaintiff's Exhibit No. P-12

headquartered in Denver Colorado where we also have our Research and Development Center.

Luzenac America mines and processes around a half-a-million tons per year generating approximately Redacted in sales.

Our major markets are talc sales to paper, polymers and paint markets……. and to a lesser degree, personal care products………

You might be interested to know that we produce all the baby powder for Johnson & Johnson – including the talc for their popular adult product, Shower-to-Shower. As an interesting aside, would you believe that Luzenac talc also goes into Cipro?? It's True!…………

SLIDE 2

Our major regulatory challenge……… a challenge I might add that Luzenac absolutely could not afford to lose ………………..came from the NTP.

The NTP was authorized by the United States Congress to coordinate interagency toxicological testing and to publish the formal "Report on Carcinogens" which comes out about every 18-24 months………. To be listed in the RoC can be

devastating to a substance because of mandatory labeling requirements by OSHA and Proposition 65 in California.

In early 2000, NTP nominated talc for possible listing in the RoC because back in the early 1990's, the NTP published the results of a 2-year talc inhalation study on rats and mice and concluded that talc caused lung tumors in female rats………

More on that in a minute.

SLIDE 3

A listing of talc in the RoC would have devastating consequences for the talc market worldwide.

First of all……we would see a virtual immediate loss of our sales to the personal care market – around $10 Million in sales in the first year.

Secondly…….because of the carcinogenic labeling requirements, we would likely suffer a deterioration of sales in all markets….perhaps anywhere from 20% to 50% of all remaining sales by year-three.

Additionally, a listing in the U.S. by NTP would likely trigger a carcinogenic status for talc in Europe and the Far East.

And finally……. because of our consumer product exposure, civil litigation would likely skyrocket.

As I mentioned, simply devastating consequences.

SLIDE 4

Now realistically….. there are some health issues with talc. For nearly 20 years, epidemiologists have been finding a weak, but persistent statistical link between the hygienic use of talc and ovarian cancer. However……. the studies are weakened by no one being able to offer any feasible “causal” explanations as to how and why talc would cause ovarian cancer……..but not a multitude of other cancers in the human anatomy.

As I mentioned, there is the 1992 rodent study by NTP, which found lung tumors in female rats. However, many other leading experts discount this finding claiming the tumors were a result of lung overload - simply too much inert dust in the lungs triggering an traumatic auto-immune response from the rats.

And finally, there is the long-held public perception that all talc contains asbestos. And even if it

doesn't, they are so similar chemically, that talc probably behaves like asbestos.

So these are some of the primary issues and concerns that served as the backdrop for the NTP review.

SLIDE 5

Okay….so here's what happened.

NTP announces in early 2000 that talc is going to be review. While this announcement catches us off guard, we are not alarmed.

But then, in October of 2000, NTP issues their draft report on talc and announces that the first two formal reviews resulted in votes to list talc as a carcinogen. The combined vote was 13-2 to list.

The entire talc industry, as well as companies like J&J were absolutely, positively, unquestionably, flabbergasted………. We simply could not believe it.

But now we had only two months to prepare for the third NTP review meeting……… a public meeting of the influential Board of Scientific Counselors Subcommittee. This occurred in December of last

year and we achieved a very dramatic turnaround. The BSC subcommittee voted 7-3 ***not*** to list talc.

And finally……we fast-forward to this past June for the fourth and final review process. We see the NTP Executive Committee took the unprecedented action to actually ***"stop"*** the review process on talc and send it back to the beginning. They did this by deferring a final vote on talc.

And make no mistake about it, they knew if they proceeded with a listing nomination for talc, Luzenac America was going to challenge them in Federal Court……and as the facts lay out, NTP would likely lose. Of that we are fairly certain!

SLIDE 6

Our successful defense strategy was threefold.

First…………we continued to work through the auspices of the CTFA – the Washington based trade association for the cosmetics industry. As you might imagine, Luzenac and Johnson & Johnson wield considerable influence on the talc subcommittee.

Secondly…….and this was our secret weapon, engage the services of the Washington based

Center for Regulatory Effectiveness, CRE. Since its formation in 1996 by several ex-high ranking officials in the OMB, CRE has grown into a nationally recognized…and relatively respected… regulatory watchdog organization. Federal agencies frequently come to them for assistance. CRE has also taken NTP to court.

And thirdly, we decided to be aggressive. This was a fight we simply could not lose. As such, we retained expert legal counsel to ensure we would have a solid foundation for a legal challenge if necessary…….it was the same firm which assisted CRE in their court battle with NTP……..and we also became very aggressive in our communication with NTP and other federal agencies. When didn't let the windows of "formal comment periods" become restrictive. We sent e-mails, faxes, overnight letters, and even telephones calls to key players in this battle….right up until hours before the final Executive Committee meeting.

And we believe these strategies paid-off.

SLIDE 7

While we certainly would have preferred a total victory – where NTP declared talc was not a human carcinogen……..we were relieved to at least get the review process "derailed" for now……….at least we have some "breathing space" to prepare a thorough, scientific defense of talc.

One of the issues we plan to focus on is demonstrating to NTP that virtually all of the epidemiology studies they previously used must be declared invalid for use in assessing talc "not containing asbestos". This will be an expansion of the "Fatal Flaw" defense Luzenac employed in the first review on talc.

Additionally, we believe the latest epidemiology study which IS valid with regard to talc quality….it's called the Gertig study……..and which also happens to be the largest study as well….. shows no increased risk of ovarian cancer. The significance of this study must be more heavily weighted than prior studies.

Any predictions at this point? Hard to say…but our hard fought victory this past year has given us some confidence and direction.

One last point……..lest we get complacent.. ………regardless of what happens with NTP, we also have to keep an eye out for IARC. IARC reviewed talc back in 1986 and concluded there was insufficient evidence of talc carcinogencity in humans. We are hoping that this NTP activity doesn't stimulate IARC conduct an "end-run" around NTP declare talc a possible human carcinogen…………..because I think you all know, we do not have the ability to become an active participant in that relatively "closed" process.

Thank you for your time.

EXHIBIT 23

Luzenac AMERICA

DENVER TECHNICAL CENTER
8985 E. NICHOLS AVE. • ENGLEWOOD, CO 80112 • USA

FACSIMILE

DATE:	March 26, 2002	FROM:	**Richard J. Zazenski** Director Product Safety
TO:	**Bill Ashton** **J&J**	PHONE:	303-643-0404
		e-MAIL	rzazensk@luzenac.com
		FAX:	303-799-8926
cc:		Number of Pages: (Including Cover Sheet)	**13 pages**

CONFIDENTIAL

Redacted

Luzenac GROUP

Plaintiff's Exhibit No. P-27

Redacted

One other note – We've been successful thus far in fending off the NTP classification of talc as being a potential human carcinogen. But we must also keep an eye out for IARC. If they decide to re-review the status of talc because of all the ovarian epidemiology studies that have been published **since 1986**, IARC can surprise us all and decide to list "talc" as a potential human carcinogen. IARC reviews are not a public debate. Unlike NTP, IARC is answerable to no one politically (they are headquartered in Lyon, France of all places). As part of the World Health Organization, they act very independently to protect the citizens of this planet from "preventable" diseases. Their threshold for required medical evidence is predictably quite minimal.

You might want to counsel your management on this potential (and not to be too complacent about the status of talc).

Attached with this fax:
1 page on IARC (who they are).
2 pages on IARC's 1986 review of talc.
8 pages on their 1996 re-review of all forms of silica.

If any pages are unclear, please contact us.

Luzenac Group

HP OfficeJet G Series G85
Personal Printer/Fax/Copier/Scanner

Fax-History Report for
TECHNICAL ASSURANCE
(908)874-1126
Mar 26 2002 8:16am

Last Fax

Date	Time	Type	Identification	Duration	Pages	Result
Mar 26	8:15am	Sent	918593924202	1:06	1	OK

Result:
OK - black and white fax
Okay color - color fax

EXHIBIT 24

Luzenac America
DENVER TECHNICAL CENTER
8985 E. NICHOLS AVE. • ENGLEWOOD, CO 80112 • USA

INTEROFFICE MEMORANDUM

DATE: September 12, 2000

TO: R. Bernstein; J. Gauntt; R. Meli

CC:

FROM: Carl E. Kollmar

SUBJECT: Cosmetics Consultant Update

Richard Dodwell has filed his Progress Report. At this stage of the project he has completed all fax and telephone surveys and interviewed Luzenac's salespeople. At this time, there appears to be two problems with the market survey. First, several major body powder players have chosen not to respond to the surveys. This is an issue we need to consider. Second, Luzenac's major cosmetics distributor, WC&D, has not been interviewed. This is because Tom Grunstra, their in-house talc expert, has been out sick for several weeks.

Although we are missing input from several major players, I think there are some basic facts coming to light:

- Health is an issue to large body powder customers - a non-issue in other segments.
- The large volume body powder segment is not growing, although the decline of the past few years appears to have bottomed out. There is some growth in other segments.
- Other than soap bars, there appear to be limited growth opportunities (new markets/new products) for talc.

In my opinion, the large volume body powder portion of this business is not growing, it is price sensitive, there is aggressive competition (supplier and customer) and the omen of health concerns/liabilities hangs over it. This does not appear to be a market of opportunity for Luzenac at this time. Opportunities for growth appear to be limited to the soap bar segment – but the health/liability concerns remain.

In the details of Dodwell's report he identifies six major areas of interest: customer concerns, market growth, pricing, health concerns, competition and responsiveness to the survey.

Plaintiff's Exhibit No. P-24

 LUZ006507

Customer Concerns

There are three major concerns expressed by customers:

- The closing of a Montana mine has caused some disruption in the market. I assume they are referring to the closing of the Beaverhead Mine and the subsequent discontinuance of the Supreme and Olympic products. Some customers are still using old stockpiled material and have either not found or tested a suitable alternate.
- The technical service from Luzenac has declined, but the rest of the service package (quality, delivery, etc.) is well regarded.
- The health issue is taken seriously by large users (mainly body powder customers), and mostly ignored by the smaller segments and packagers.

Market Growth

- The market is growing in many sectors, but remaining static in the body powder applications. It appears that business in the body powder segment is merely shifting around, particularly amongst the packagers.
- There are no new applications for talc, except some work in soap bars. One soap bar company, P&G, appears ready to move to customer trials and market testing.
- Surface treated talcs hold some promise, but more application research by the talc suppliers is needed to demonstrate the merits.

Pricing

- Pricing is an issue to the large volume consumers, but not an issue with the smaller higher value segments where quality, technical service and product performance are the key requirements expected of a supplier.

Health Concerns

- Some companies label their products "Talc Free", but this is more for advertising and sales promotion than to address health concerns.
- The general public is not aware of any health issues regarding talc.

Competition

- Most of the decline in talc usage has occurred during the past 5 years and has bottomed out.
- There are no serious replacement threats to talc. "Wheat", "Oat Flour" and "Corn Starch" are not direct threats to talc since they were introduced under the "natural" and "organic" banners. Although they have replaced some talc, they have proved to be less than ideal and are now more often used in blends with talc.

- Not many customers expressed a preference for a talc supplier, but those that did mentioned Luzenac.

Responsiveness to Survey

Several companies would not respond unless the survey sponsor was revealed – this was the over-riding concern of those that did not respond to the surveys. In addition, large body powder users were reluctant to respond to this survey because of health liability concerns and, to a lesser extent, because their companies have a policy against revealing confidential information.

At this point, Dodwell has contacted 96 companies and achieved a level of response slightly above 35% - I think this is better than expected.

- Twenty-one companies were called twice with no response and appear to use their voice mail as a screening tool. They include Coty, Kolmar Labs, Maybelline, Revlon (NJ), Colgate Palmolive and Amway.
- Eleven companies generally refused to participate in the survey. This group included J&J, MK Packaging, Thornton, Lancome/Cosmair, Lander, Estee Lauder and Revlon (NC).

Obviously, we are missing an input from several of the major players. To get their input we would have to either reveal the survey sponsor and/or raise their level of interest to respond. Their level of interest can be raised by appealing to their self-interest – "if I don't respond to this survey it may affect my supply of talc". In either case, a personal visit may be required. As I mentioned during my update at the last Management Meeting, revealing the sponsor or raising their level of interest is a double-edged sword – it either brings forth the desired response out of self-interest, or it generates a concern over the supplier's viability and loyalty to the market. It could cause them to consider other talcs or talc alternatives. At this point, I would recommend that Dodwell make no further extraordinary efforts to pursue those who are not responding. This can be a topic of discussion when Dodwell presents his findings at the October 5th meeting in Denver.

EXHIBIT 25

to be informed promptly and effectively of important new knowledge regarding nutritional and health benefits of food. Third, these amendments to this health claim will ensure that scientifically sound nutritional and health information regarding the benefits of fruit and vegetable intake and reduction of CHD risk can be provided to consumers as soon as possible. The past few editions of the DGA have been moving away from a focus on total fat and have instead communicated to consumers the need to focus on type of fat consumed instead of total amount of fat. Recent editions of the DGA have also encouraged increased intake of fruits and vegetables for a healthful diet. Prompt issuance of an interim final rule that reflects the current recommendations is necessary for consumers to be able to have the most current information on nutrition and diet. Consumers will be better able to construct healthful diets if they have prompt access to information that is consistent with the current recommendations on fat content and on consumption of fruits and vegetables. Therefore, we are using the authority in section 403(r)(7)(A) of the FD&C Act to issue an interim final rule amending the general requirements for the health claim for dietary saturated fat and cholesterol and risk of CHD and to make the interim final rule effective immediately.

This regulation is effective upon publication in the **Federal Register**. We invite public comment on this interim final rule. We will consider modifications to this interim final rule based on comments made during the comment period. We will address comments and confirm or amend the interim final rule in a final rule.

X. References

The following references are on display in the Division of Dockets Management (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at *http://www.regulations.gov*. FDA has verified the Web site addresses, as of the date this document publishes in the **Federal Register**, but Web sites are subject to change over time.

1. Liu, S., J.E. Manson, I.M. Lee, et al. ''Fruit and Vegetable Intake and Risk of Cardiovascular Disease: The Women's Health Study.'' *The American Journal of Clinical Nutrition*, 72: 922–928, 2000.

2. Appel, L.J., T.J. Moore, E. Obarzanek, et al. ''A Clinical Trial of the Effects of Dietary Patterns on Blood Pressure.'' DASH Collaborative Research Group. *The New England Journal of Medicine*, 336: 1117–1124, 1997.

3. U.S. Department of Health and Human Services and U.S. Department of Agriculture. ''Dietary Guidelines for Americans, 2010. 7th Edition,'' 2010. Available at *http://health.gov/dietaryguidelines/2010/*.

4. ''Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report.'' *Circulation*, 106: 3143–3421, 2002.

5. U.S. Department of Health and Human Services and U.S. Department of Agriculture. ''2015–2020 Dietary Guidelines for Americans, 8th Edition,'' December 2015. Available at *http://health.gov/dietaryguidelines/2015/guidelines/*.

6. U.S. Department of Health and Human Services and U.S. Department of Agriculture. ''Nutrition and Your Health, Dietary Guidelines for Americans,'' 2000. Available at *http://health.gov/dietaryguidelines/2000.asp*.

7. U.S. Department of Health and Human Services and U.S. Department of Agriculture. ''Dietary Guidelines for Americans, 2005. 6th Edition,'' 2005. Available at *http://health.gov/dietaryguidelines/dga2005/document/default.htm*.

8. Institute of Medicine (IOM) of the National Academies. ''Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients).'' Chapter 8, ''Dietary Fats: Total Fat and Fatty Acids,'' 2002.

9. FDA/CFSAN, Food Labeling: Health Claims; Dietary Saturated Fat and Cholesterol and Risk of Coronary Heart Disease, Regulatory Impact Analysis, FDA–2013–P–0047.

List of Subjects in 21 CFR Part 101

Food labeling, Nutrition, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 101 is amended as follows:

PART 101—FOOD LABELING

■ 1. The authority citation for part 101 continues to read as follows:

Authority: 15 U.S.C. 1453, 1454, 1455; 21 U.S.C. 321, 331, 342, 343, 348, 371; 42 U.S.C. 243, 264, 271.

■ 2. Section 101.75 is amended by revising paragraphs (c)(1) and (c)(2)(ii) to read as follows:

§ 101.75 Health claims: dietary saturated fat and cholesterol and risk of coronary heart disease.

* * * * *

(c) * * *

(1) All requirements set forth in § 101.14 shall be met, except § 101.14(e)(6) with respect to a raw fruit or vegetable.

(2) * * *

(ii) *Nature of the food.* (A) The food shall meet all of the nutrient content requirements of § 101.62 for a ''low saturated fat'' and ''low cholesterol'' food.

(B) The food shall meet the nutrient content requirements of § 101.62 for a ''low fat'' food, unless it is a raw fruit or vegetable; except that fish and game meats (*i.e.*, deer, bison, rabbit, quail, wild turkey, geese, and ostrich) may meet the requirements for ''extra lean'' in § 101.62.

* * * * *

Dated: December 9, 2016.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2016–29997 Filed 12–16–16; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 878, 880, and 895

[Docket No. FDA–2015–N–5017]

RIN 0910–AH02

Banned Devices; Powdered Surgeon's Gloves, Powdered Patient Examination Gloves, and Absorbable Powder for Lubricating a Surgeon's Glove

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA or Agency) has determined that Powdered Surgeon's Gloves, Powdered Patient Examination Gloves, and Absorbable Powder for Lubricating a Surgeon's Glove present an unreasonable and substantial risk of illness or injury and that the risk cannot be corrected or eliminated by labeling or a change in labeling. Consequently, FDA is banning these devices.

DATES: This rule is effective on January 18, 2017.

ADDRESSES: For access to the docket to read background documents or comments received, go to *https://www.regulations.gov* and insert the docket number found in brackets in the

heading of this final rule into the ''Search'' box and follow the prompts, and/or go to the Division of Dockets Management, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT:

Michael J. Ryan, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 1615, Silver Spring, MD 20993, 301–796–6283, email: *michael.ryan@fda.hhs.gov*.

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Executive Summary

A. Purpose and Coverage of the Final Rule

Medical gloves play a significant role in the protection of both patients and health care personnel in the United States. Health care personnel rely on medical gloves as barriers against transmission of infectious diseases and contaminants when conducting surgery, as well as when conducting more limited interactions with patients. Various types of powder have been used to lubricate gloves so that wearers could don the gloves more easily. However, the use of powder on medical gloves presents numerous risks to patients and health care workers, including inflammation, granulomas, and respiratory allergic reactions.

A thorough review of all currently available information supports FDA's conclusion that powdered surgeon's gloves, powdered patient examination gloves, and absorbable powder for lubricating a surgeon's glove should be banned. FDA has concluded that the risks posed by powdered gloves, including health care worker and patient sensitization to natural rubber latex (NRL) allergens, surgical complications related to peritoneal adhesions, and other adverse health events not necessarily related to surgery, such as inflammatory responses to glove powder, are important, material, and significant in relation to the benefit to public health from their continued marketing. FDA has carefully evaluated the risks and benefits of powdered gloves and the risks and benefits of the state of the art, which includes viable non-powdered alternatives that do not carry any of the risks associated with glove powder, and has determined that the risk of illness or injury posed by powdered gloves is unreasonable and substantial. Further, FDA believes that this ban would likely have minimal economic and shortage impact on the health care industry. Thus, a transition to alternatives in the marketplace should not result in any detriment to public health.

This rule applies to powdered patient examination gloves, powdered surgeon's gloves, and absorbable powder for lubricating a surgeon's glove. This includes all powdered medical gloves except powdered radiographic protection gloves. Because we are not aware of any powdered radiographic protection gloves that are currently on the market, FDA lacks the evidence to determine whether the banning standard would be met for this particular device. The ban does not apply to powder used in the manufacturing process (*e.g.,* former-release powder) of non-powdered gloves, where that powder is not intended to be part of the final finished glove. Finished non-powdered gloves are expected to include no more than trace amounts of residual powder from these processes, and the Agency encourages manufacturers to ensure finished non-powdered gloves have as little powder as possible. In our 2008 Medical Glove Guidance Manual (Ref. 1), we recommended that non-powdered gloves have no more than 2 milligrams (mg) of residual powder and debris per glove, as determined by the Association for Testing and Materials (ASTM) D6124 test method (Ref. 2). The Agency continues to believe this amount is an appropriate maximum level of residual powder. The ban also does not apply to powder intended for use in or on other medical devices, such as condoms. FDA has not seen evidence that powder intended for use in or on other medical devices, such as condoms, presents the same public health risks as that on powdered medical gloves.

B. Summary of the Major Provisions of the Final Rule

In this final rule, FDA is banning the following devices: (1) Powdered surgeon's gloves, (2) powdered patient examination gloves, and (3) absorbable powder for lubricating a surgeon's glove. Because the classification regulations for these device types do not distinguish between powdered and non-powdered versions, FDA is amending the descriptions of these devices in the regulations to specify that the regulations for patient examination and surgeon's gloves will apply only to non-powdered gloves while the powdered version of each type of glove will be added to the listing of banned devices in the regulations.

Many comments requested that FDA revise the scope of the ban to include all NRL gloves. Many comments from industry requested that the proposed effective date be extended beyond 30 days after the date of publication of the final rule. Of the comments that do not support the ban, commenters noted the need for powdered gloves to aid in donning gloves and tactile sense and the reduced risks associated with current powdered gloves that have less powder. The remaining comments are not clearly in support or opposition to the proposal.

C. Legal Authority

Powdered surgeon's gloves, powdered patient examination gloves, and absorbable powder for lubricating a surgeon's glove are defined as devices under section 201(h) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 321(h)). Section 516 of the FD&C Act (21 U.S.C. 360f) authorizes FDA to ban a device if it finds, on the basis of all available data and information, that the device presents substantial deception or unreasonable and substantial risks of illness or injury, which cannot be corrected by labeling or a change in labeling. This rule amends 21 CFR 878.4460, 878.4480, 880.6250, 895.102, 895.103, and 895.104. FDA's legal authority to modify §§ 878.4460, 878.4480, 880.6250, 895.102, 895.103, and 895.104 arises from the device and general administrative provisions of the FD&C Act (21 U.S.C. 352, 360f, 360h, 360i, and 371).

D. Costs and Benefits

The final rule is expected to provide a positive net benefit (estimated benefits minus estimated costs) to society. Banning powdered glove products is not expected to impose any costs to society, but is expected to reduce the number of adverse events associated with using powdered gloves. The primary public health benefit from adoption of the rule would be the value of the reduction in adverse events associated with using powdered gloves. The Agency estimates maximum total annual net benefits to range between $26.8 million and $31.8 million.

II. Background

A. Need for the Regulation/History of the Rulemaking

On March 22, 2016, FDA issued a proposed rule to ban powdered surgeon's gloves, powdered patient examination gloves, and absorbable powder for lubricating a surgeon's glove (81 FR 15173). Section 516(a)(1) of the FD&C Act authorizes FDA to ban a device intended for human use by regulation if it finds, on the basis of all available data and information, that such a device ''presents substantial deception or an unreasonable and substantial risk of illness or injury.'' For a more detailed discussion of the banning standard, we refer you to the preamble of the proposed rule. FDA issued the proposed regulation because it determined that powdered surgeon's gloves, powdered patient examination gloves, and absorbable powder for lubricating a surgeon's glove present an unreasonable and substantial risk of illness or injury and that the risk cannot be corrected or eliminated by labeling or a change in labeling.

The preamble to the proposed rule describes the history of powdered gloves and the citizen petitions received by the Agency that request a ban on powdered gloves. We refer readers to that preamble for information about the development of the proposed rule. The level and types of risk presented by powdered gloves varies depending on the composition and intended use of the glove. In aggregate, the risks of powdered gloves include severe airway inflammation, hypersensitivity reactions, allergic reactions (including asthma), allergic rhinitis, conjunctivitis, dyspnea, as well as granuloma and adhesion formation when exposed to internal tissue. We refer readers to the preamble of the proposed rule for details on the level and types of risks presented by powdered gloves. The benefits of powdered gloves appear to only include greater ease of donning and doffing, decreased tackiness, and a degree of added comfort, which FDA believes are nominal when compared to the risks posed by these devices.

The state of the art of both surgeon's and patient examination gloves includes non-powdered alternatives that provide similar performance as the various powdered glove types do. That is, there are many non-powdered gloves available that have the same level of protection, dexterity, and performance. Thus, based on a careful evaluation of the risks and benefits of powdered gloves and the risks and benefits of the current state of the art, which includes readily available alternatives that carry none of the risks posed by powdered gloves, FDA has determined that the standard to ban powdered gloves has been met, and that it is appropriate to issue this ban.

Finally, as discussed in the proposed rule, FDA also determined the ban should apply to devices already in commercial distribution and devices already sold to the ultimate user, as well as to devices that would be sold or distributed in the future (see 21 CFR 895.21(d)(7)). This means that powdered gloves currently being used in the marketplace would be subject to this ban and adulterated under section 501(g) of the FD&C Act (21 U.S.C. 351(g)), and thus subject to enforcement action.

B. Summary of Comments to the Proposed Rule

The Agency requested public comments on the proposed rule, and the comment period closed on June 20, 2016. The Agency received approximately 100 comment letters on the proposed rule by the close of the comment period, each containing one or more comments on one or more issues. We received comments from a cross-section of patients and consumers, medical professionals, device manufacturers, and professional and trade associations. A majority of the comments supported the objectives of the rule in whole or in part, while a minority of the comments opposed the objectives of the rule. Some comments suggested changes to specific elements of the proposed rule or requested clarification of matters discussed in the proposed rule. See Section IV for the description of comments on the proposed rule and FDA's responses.

C. General Overview of the Final Rule

FDA published a proposed rule to ban powdered surgeon's gloves, powdered patient examination gloves, and absorbable powder for lubricating a surgeon's glove, because FDA determined that these devices present an unreasonable and substantial risk of illness or injury and that the risk cannot be corrected or eliminated by labeling or a change in labeling (81 FR 15173).

In this final rule, FDA is banning the following devices: (1) Powdered surgeon's gloves (21 CFR 878.4460), (2) powdered patient examination gloves (21 CFR 880.6250), and (3) absorbable powder for lubricating a surgeon's glove (21 CFR 878.4480). Because the classification regulations for these device types do not distinguish between powdered and non-powdered versions, FDA is amending the descriptions of these devices in the regulations to specify that the regulations for surgeon's gloves (21 CFR 878.4460) and patient examination gloves (21 CFR 880.6250) will apply only to non-powdered gloves while the powdered version of each type of glove will be added to 21 CFR part 895, subpart B—Listing of Banned Devices.

D. Clarifying Changes to the Rule

While FDA believes that the preamble to the proposed rule was clear that the proposed ban would apply to all powdered surgeon's gloves and all powdered patient examination gloves, in reviewing the terminology used in the proposed additions to 21 CFR part 895, FDA determined that term ''synthetic latex'' would not cover every type of non-NRL material that is used to manufacture powdered gloves. It was not FDA's intent to limit the ban to only powdered NRL and powdered synthetic latex gloves, and we believe that this intent was clear from the content of the preamble to the proposed rule, which stated that the ban ''would apply to all powdered gloves except powdered radiographic protection gloves.'' As such, FDA has now revised the identification in this final rule to clarify that the ban applies to all powdered surgeon's gloves and powdered patient examination gloves without reference to the type of material from which they are made. Additionally, the identification of non-powdered surgeon's gloves and non-powdered patient examination gloves is also being revised to remove reference to material.

III. Legal Authority

Powdered surgeon's gloves, powdered patient examination gloves, and absorbable powder for lubricating a surgeon's glove are defined as medical devices under section 201(h) of the FD&C Act (21 U.S.C. 321). Section 516 of the FD&C Act (21 U.S.C. 360f) authorizes FDA to ban a device if it finds, on the basis of all available data and information, that the device

presents substantial deception or unreasonable and substantial risks of illness or injury, which cannot be corrected by labeling or a change in labeling. This rule amends §§ 878.4460, 878.4480, 880.6250, 895.102, 895.103, and 895.104. FDA's legal authority to modify §§ 878.4460, 878.4480, 880.6250, 895.102, 895.103, and 895.104 arises from the device and general administrative provisions of the FD&C Act (21 U.S.C. 352, 360f, 360h, 360i, and 371).

IV. Comments on the Proposed Rule and FDA's Responses

A. Introduction

We received approximately 100 comment letters on the proposed rule by the close of the comment period, each containing one or more comments on one or more issues. We received comments from a cross-section of patients and consumers, medical professionals, device manufacturers, and professional and trade associations. A majority of the comments supported the objectives of the rule in whole or in part, while a minority of the comments opposed the objectives of the rule. Some comments suggested changes to specific elements of the proposed rule or requested clarification of matters discussed in the proposed rule.

We describe and respond to the comments in section IV.B through E. We have numbered each comment to help distinguish between different comments. We have grouped similar comments together under the same number, and, in some cases, we have separated different issues discussed in the same comment and designated them as distinct comments for purposes of our responses. The number assigned to each comment or comment topic is purely for organizational purposes and does not signify the comment's value or importance or the order in which comments were received.

B. Description of General Comments and FDA Response

Many comments made general remarks supporting or opposing the proposed rule without focusing on a particular proposed provision. In the following paragraphs, we discuss and respond to such general comments.

(Comment 1) Many comments support the proposed ban on powdered patient examination gloves and powdered surgeon's gloves. These comments from individual consumers, health care professionals, academia, and industry highlight several risks of the continued use of powdered gloves, including, among others, allergic reactions, post-operative adhesions, and delayed wound healing.

(Response 1) FDA agrees with these comments. After further review of all available information and the comments submitted to the proposed rule, FDA has concluded that the public's exposure to the risks of powdered gloves is unreasonable and substantial in relation to the nominal public health benefit derived from the continued marketing of these devices, especially when considering the benefits and risks posed by readily available alternative devices. Therefore, FDA has determined that the standard for a ban on these devices has been met.

C. Description of Comments That Oppose the Regulation and FDA Response

FDA received some comments that oppose the proposed ban on powdered patient examination gloves and powdered surgeon's gloves for various reasons. We address each of these reasons for opposition in this section. After reviewing these comments, FDA has determined that the standard to ban powdered gloves has been met, and that it is appropriate to issue this ban. We are finalizing the ban with only clarifying changes.

(Comment 2) Comments oppose the proposed ban on powdered patient examination gloves and powdered surgeon's gloves because of difficulty donning or doffing non-powdered gloves. Two commenters specifically discuss hyperhidrosis with claims that it can add to the difficulty donning and doffing non-powdered gloves. One commenter has asserted that double-gloving is more difficult when using non-powdered gloves.

(Response 2) As described in the preamble of the proposed rule, we have concluded that the benefit of ease of donning or doffing powdered gloves is generally nominal (Ref. 3) in comparison to the risks posed by the continued marketing of powdered gloves, which, among others, include severe airway inflammation, hypersensitivity reactions, and allergic reactions (including asthma). Also, as noted in the proposed rule, a study of various brands of powdered and non-powdered NRL gloves by Cote et al. found that there are non-powdered latex gloves that are easily donned with wet or dry hands with relatively low force compared to the forces required to don powdered latex examination gloves (Ref. 3). Thus, FDA has considered ease of donning and doffing as a benefit as it applies within the banning standard, and has determined that the standard is met.

(Comment 3) Comments oppose the proposed ban on powdered patient examination gloves and powdered surgeon's gloves because of difficulty donning non-powdered gloves, leading to greater propensity of non-powdered gloves to tear. Some of these comments express concern that the reduced ability to separate the opening of a non-powdered glove or the greater propensity of non-powdered gloves to tear could potentially lead to a higher degree of contamination and post-procedure infections.

(Response 3) FDA disagrees with the assertion that non-powdered gloves have a higher propensity to tear and thus disagrees that use of non-powdered gloves presents a greater risk of contamination, post-procedure infections, or exposure of the user to blood. FDA does not believe there is compelling evidence to support the assertion that non-powdered gloves have a higher propensity to tear. Korniewicz, et al., determined that the presence of powder did not affect the durability of gloves or enhance glove donning (Ref. 4). Although Kerr, et al., identified a statistically significant difference in the durability of non-powdered vinyl gloves compared to powdered vinyl gloves, this difference may be attributed to glove type, manufacturer, and the fingernail length of users rather than the presence or absence of powder (Ref. 5). This study also found that vinyl gloves in general are less durable and have a greater propensity to tear compared to nitrile, neoprene, and latex gloves. Furthermore, as discussed in the response to comment 4, several studies have found that alternatives to non-powdered NRL gloves, such as nitrile and neoprene gloves, offer the same level of protection against contamination and exposure to blood as powdered NRL gloves (Refs. 5, 6, 7, 8, 9, and 10). Therefore, FDA has determined that suitable alternatives to powdered gloves are readily available in the marketplace.

(Comment 4) Commenters oppose the proposed ban on powdered patient examination gloves and powdered surgeon's gloves because the fit of powdered gloves is more comfortable than non-powdered gloves. Some of these comments assert that the reduced fit of non-powdered gloves inhibits the tactile sensation necessary to perform medical procedures.

(Response 4) FDA disagrees with the assertion that non-powdered gloves inhibit the tactile sensation necessary to perform medical procedures. The ban does not include non-powdered NRL gloves, which offer the same

performance characteristics of powdered NRL gloves, and several studies have found that alternatives, such as nitrile and neoprene gloves, offer the same level of protection, dexterity, and performance as NRL gloves (Refs. 5, 6, 7, 8, 9, and 10). Furthermore, the numerous risks posed by the continued marketing of powdered gloves outweigh the benefit of whatever additional level of comfort is provided from using powdered gloves instead of the non-powdered alternatives that carry none of these risks.

(Comment 5) Some comments oppose the proposed ban on powdered patient examination gloves and powdered surgeon's gloves, citing a lack of scientific evidence that gloves with reduced powder content, as those in use today, have the same risks as previously used gloves that had higher powder content.

(Response 5) FDA agrees that the maximum residual level of powder on powdered gloves is less than earlier types of powdered gloves. Historically, powdered medical gloves contained powder levels ranging from 50 to over 400 mg of powder per glove. Effective in 2002, the ASTM International recommended limits on powder levels is 15 mg per square decimeter for surgical gloves (ASTM D3577–2001) (Ref. 11) and 10 mg per square decimeter for patient examination gloves (ASTM D3578) (Ref. 12). As a result, FDA believes that gloves in use after 2002 follow these recommended limits and generally have lower powder content than earlier types of powdered gloves. Even so, several studies indicate that gloves with reduced powder levels continue to present unreasonable and substantial risks to patients and health care workers. For instance, a study conducted on the incidence of skin reactions for Greek endodontists from 2006 to 2012 found that glove powder accounted for the majority of skin reactions, and the replacement of powdered NRL gloves with non-powdered gloves resolved the majority of the adverse reactions (Ref. 13). Similarly, the risks of powdered gloves persist in non-clinical studies using gloves with reduced powder content, as demonstrated by the 2013 finding that surgeries performed with powdered gloves increased the number, density, and fibrotic properties of peritoneal adhesions in rats compared with surgeries performed with non-powdered gloves (Ref. 14). Also, the reduction in cases of NRL-induced occupational contact urticaria coincided with French hospitals transitioning to non-powdered gloves after 2004–2005 (Ref. 13). Finally, FDA is not aware of any report in the literature that supports the assertion that currently marketed powdered gloves with lower powder content reduce the risks presented by powdered gloves (Ref. 15). In summary, FDA concludes that the risks of powder continue to be unreasonable and substantial for currently marketed powdered gloves despite lower powder content than previous generations of powdered gloves.

(Comment 6) Two comments oppose the proposed ban on powdered patient examination gloves and powdered surgeon's gloves, because the commenters believe a warning on the risks of powdered gloves is sufficient to mitigate the risks posed by these devices.

(Response 6) As described in Section IV of the proposed rule, FDA has determined that no change in labeling could correct the risk of illness or injury presented by the continued use of these devices. Powdered gloves have additional or increased risks to health compared to non-powdered gloves related to the spread of powder, and the fact that powder-transported contaminants such as NRL allergens can become aerosolized. Exposure to powder or latex allergens presents significant risks to health care workers and patients when inhaled or when exposed to internal tissue during oral, vaginal, gynecological, and rectal exams. Although labeling can raise awareness of these risks, we conclude that labeling cannot effectively mitigate these risks because it cannot prohibit the spread of glove powder or powder-transported contaminants. In addition, an important aspect of these devices is their ability to affect persons other than the individual who decides to wear or use them. For example, patients often do not know the type of gloves being worn by the health care professional treating them, but are still exposed to the potential dangers. Similarly, glove powder's ability to aerosolize and carry NRL proteins exposes individuals to harm via inhalation or surface contact. Thus, some of the risks posed by glove powder can impact persons completely unaware or unassociated with its employment and without the opportunity to consider the devices' labeling. Because of this inherent quality, adequate directions for use or warnings cannot be written that would provide reasonable assurance of the safe and effective use of these devices for all persons that might come in contact with them.

Due to the ability of powder to affect people who would not have an opportunity to read warning labels, and because potential warning labels would raise awareness of the risks, but would not eliminate the risks posed by glove powder, FDA has determined no label or warning can correct the risks posed by these devices.

(Comment 7) One comment opposes the proposed ban on powdered patient examination gloves and powdered surgeon's gloves, because the solvent used to remove powder during the manufacture of non-powdered gloves may cause adverse reactions to the glove user.

(Response 7) FDA is not aware of any report in the literature that supports the assertion of widespread adverse reactions to solvent used in the manufacturing process. Non-powdered patient examination and surgeon's gloves require premarket notification (510(k)) submissions prior to marketing. During the review of these submissions, FDA evaluates the final finished glove, including manufacturing solvents that are present on the final glove. FDA recommends that manufacturers conduct and submit skin irritation and dermal sensitization studies in these submissions to evaluate potential issues with components, including manufacturing solvents (Ref. 1). Although individual hypersensitivity reactions to different materials may occur, FDA has been unable to find evidence in the literature of hypersensitivity to typical glove manufacturing materials other than glove powder or NRL. However, Palosuo, et al., reports that the use of hand sanitizers containing isopropyl alcohol prior to donning gloves could cause dermatitis reaction if the gloves are donned before the alcohol dries (Ref. 16). The occurrence of this reaction is unrelated to the manufacture of non-powdered gloves and unrelated to the use of non-powdered gloves as an alternative to powdered gloves. Given the lack of evidence of adverse reactions to solvents used in the manufacturing of non-powdered gloves, and the established evidence demonstrating the risks of powdered glove use, FDA continues to believe that powdered gloves and glove powder meet the banning standard.

(Comment 8) Several comments oppose the proposed ban on powdered patient examination gloves and powdered surgeon's gloves due to the expectation that users will ultimately have to pay more for medical gloves once the ban is finalized, because the cost of non-powdered gloves is currently higher than the cost of powdered gloves.

(Response 8) We do not find any evidence to support the claims that

current prices of non-powdered gloves are significantly higher than powdered gloves. As we stated in the preliminary regulatory impact analysis (PRIA), extensive searches of glove distributor pricing indicate that non-powdered gloves have become as affordable as powdered gloves. Our searches also revealed that the market is saturated with alternatives to powdered gloves, resulting in downward pressure on the prices of non-powdered gloves. In addition, the share of powdered medical gloves sales has been declining since at least 2000 while total sales of all disposable medical gloves have increased (Ref. 17). We would not expect this trend to be occurring without regulatory action if users of disposable medical gloves faced significantly higher prices for switching to non-powdered gloves. We therefore do not find it necessary to update our analysis based on these comments.

(Comment 9) We received one comment that disagrees with our determination that the availability of examination and surgical gloves would not be reduced.

(Response 9) We do not find any evidence to support these claims. As we stated in the PRIA, research shows only 7 percent of total sales of examination and surgical gloves to medical workers were projected to be from powdered gloves in 2010 (Ref. 17). Global Industry Analysts (GIA) projected the share of powdered disposable medical gloves sales to decrease to 2 percent in 2015, while total sales of all disposable medical gloves continue to increase (Ref. 17). We would not expect this trend to be occurring without regulatory action if there were a reduction in the availability of disposable examination and surgical gloves. We therefore do not find it necessary to update our analysis based on these comments.

(Comment 10) Commenters suggest there would be a loss in consumer utility due to the preference some medical workers may have for powdered gloves due to comfort and ease of use.

(Response 10) We stated in the PRIA that the remaining 7 percent continuing to use these powdered gloves may experience utility loss from the removal of powdered gloves from the market (Ref. 17). The potential loss in consumer utility would be due to the perceived loss in comfort from powdered gloves users switching to non-powdered gloves. However, as the GIA report shows, there has been a downward trend in total sales of powdered gloves since at least the year 2000 while total sales of all disposable medical gloves has increased (Ref. 17). We would not expect this trend to be occurring without regulatory action if the loss in consumer utility to current medical workers were substantial. Korniewicz et al. reported no loss in consumer satisfaction in a sample of operating room staff switching to non-powdered surgical gloves (Ref. 4). We have not estimated this potential burden, but the evidence described here suggests that any burden would not be substantial. Further, even having considered that some degree of consumer comfort may be lost by banning powdered gloves, FDA continues to believe that this benefit is considerably outweighed by the numerous risks posed by powdered gloves.

(Comment 11) One comment opposes the proposed ban on powdered patient examination gloves and powdered surgeon's gloves, because the risks identified for powdered gloves are due to contaminants, such as pesticides and herbicides, in the powder that would not be present if the powder were manufactured in the United States.

(Response 11) FDA disagrees with the assertion that contaminated powder is the source of the risks identified for powdered gloves. FDA's proposal to ban powdered gloves and glove powder is based on various studies on the risks of powdered gloves due to the properties of the powder itself. Powdered gloves have additional or increased risks to health compared to non-powdered gloves. For example, powder on NRL gloves can aerosolize latex allergens, resulting in sensitization to latex and allergic reactions. Latex sensitization and allergic reactions are unrelated to any potential presence of manufacturing contaminants, such as pesticides and herbicides. Additional risks of powdered gloves include severe airway inflammation, conjunctivitis, dyspnea, as well as granuloma and adhesion formation when exposed to internal tissue. FDA's assessment of the available literature and information indicates that these risks are attributable to the powder itself, as opposed to any potential presence of manufacturing contaminants, such as pesticides and herbicides.

In addition, the powder used on powdered gloves is required to comply with FDA's Quality System regulation, which includes requirements for quality and inspection for the final finished gloves that protect against the introduction of contaminated devices into commerce. Among other requirements, device manufacturers must establish and maintain procedures to prevent contamination of equipment or product by substances that could reasonably be expected to have an adverse effect on product quality (21 CFR 820.70(e)). FDA's Quality System regulation applies to gloves and glove powder sold in the United States, regardless of the manufacturing location.

D. Description of Comments on Scope of Ban and FDA Response

FDA received several comments requesting revision of the scope of the ban. The scope of the proposed ban includes powdered surgeon's gloves, powdered patient examination gloves, and absorbable powder for lubricating a surgeon's glove. The glove types include all powdered patient examination and surgeon's gloves, including NRL and synthetic latex gloves. In the following paragraphs, we discuss and respond to comments requesting revision of the scope of the ban. We are finalizing the ban without change to the scope, but clarifying that all powdered patient examination gloves and powder surgical gloves are banned, regardless of the material from which they are made.

(Comment 12) Several comments identify risks that result from the use of powdered and non-powdered NRL gloves. These comments request FDA to extend the ban to all NRL gloves, both powdered and non-powdered.

(Response 12) Unlike with powdered latex gloves, which have the ability to aerosolize glove powder and carry allergenic proteins, FDA believes the risk of allergic reaction to non-powdered NRL gloves, which affects the user and patients in direct contact with the glove, is adequately mitigated through already-required labeling that alerts users to this risk. NRL gloves must include a statement to alert users to the risk of allergic reactions caused by NRL (21 CFR 801.437). Further, several studies have indicated that the use of non-powdered NRL gloves reduces the risk of sensitization to allergenic NRL proteins and the number of allergic reactions experienced by those who are already sensitized (Refs. 18, 19, and 20). FDA believes that these study results, when considered alongside the risk mitigation that follows from FDA's required labeling for NRL products, demonstrates that non-powdered latex gloves can be safely used with appropriate caution for latex-sensitive patients and health care workers. Therefore, FDA has determined not to ban the use of all NRL gloves.

(Comment 13) Several comments raise the issue of life threatening latex allergy events that result from various uses of NRL gloves including food preparation and food service. Several of these comments assert that the Agency should broaden the scope of the ban to cover all

NRL gloves for all uses including food preparation and food service.

(Response 13) We have concluded that it is not appropriate to address a proposal to ban gloves used for food preparation because these gloves do not meet the definition of a device under section 201(h) of the FD&C Act and are thus not subject to section 516 of the FD&C Act (21 U.S.C. 360f), which provides the statutory authority to ban devices within FDA's authority to regulate such products.

(Comment 14) One comment asserts that the ban on powdered gloves should not apply to dental practice, because the risks are not applicable to dental practice.

(Response 14) FDA disagrees with the assertion that the risks of powdered gloves are not applicable to dental practice. Dentists and dental patients face the same risks as other medical practices in terms of the potential for powder exposure to open cavities or open wounds, and for powder, if used with NRL gloves, to carry protein allergens. Several studies documenting the risks of powdered gloves in dental practices have been conducted, including Saary, et al., which identified that changing to low-protein and non-powdered NRL gloves reduced NRL allergy in dental students (Ref. 18). In addition, Charous et al., reported in 2000 that a dental office was able to reduce airborne NRL antigen levels to undetectable levels with the exclusive use of non-powdered NRL gloves, permitting a highly sensitized staff member to continue to work there (Ref. 21). These studies, among others (Refs. 13 and 22), indicate that the risks of powdered medical gloves apply to dental practice. Therefore, FDA has determined that the scope of the ban on powdered medical gloves should continue to include powdered gloves used in dental practice.

E. Description of Other Specific Comments and FDA Response

Many comments made specific remarks requesting clarification or revision to the proposed rule. In the following paragraphs, we discuss and respond to such specific comments.

(Comment 15) A number of comments request extension of the effective date of the ban. The proposed rule included a proposed effective date of 30 days after publication of the final rule for all devices, including those already in commercial distribution. The comments suggest a range of effective dates of 90 days to 18 months after publication of the final rule and assert that a longer transition period is necessary to allow existing inventory to flow through the supply chain to providers and patients.

(Response 15) FDA is not extending the effective date of the ban for devices already in commercial distribution. We have concluded that powdered surgeon's gloves, powdered patient examination gloves, and absorbable powder for lubricating a surgeon's glove present an unreasonable and substantial risk of illness or injury and that the risk cannot be corrected or eliminated by labeling or a change in labeling. The continued marketing of these devices beyond the 30 day effective date would allow for the continued sale and purchase of devices that FDA has determined present an unreasonable and substantial risk to patients and health care workers. Therefore, FDA does not believe that it is in the best interest of the public health to extend the effective date for devices already in commercial distribution. In order to minimize the risk of continued exposure of health care workers and patients to these devices, the effective date for devices remains 30 days after the date of publication of this final rule.

(Comment 16) One comment requests that FDA not extend the effective date of the ban to allow companies to deplete their inventory of the devices.

(Response 16) As described in the response to comment 15, FDA agrees that it is in the best interest of the public health to not extend the effective date of the ban for devices already in commercial distribution. Therefore, the effective date of the ban for devices already in commercial distribution remains at 30 days after the date of publication of the final rule.

(Comment 17) A few comments request recommendations on the means of disposal or recycling of powdered gloves.

(Response 17) FDA recommends that unused inventories of powdered medical gloves remaining at domestic manufacturing and distribution locations be disposed of in accordance with standard industry practices. Unused supplies at hospitals, outpatient centers, clinics, medical and dental offices, other service delivery points (nursing homes, etc.), and in the possession of end users, will need to be disposed of according to established procedures of the local community's solid waste management system. Established procedures for these materials typically involve disposal in landfills or incineration. FDA has concluded that this final rule will not have a significant impact on the human environment. (See Section VII. Analysis of Environmental Impact.)

(Comment 18) One comment requests clarification on whether after the effective date of the ban the Agency will permit a manufacturer to export powdered medical gloves that are already physically located at distribution centers in the United States.

(Response 18) After the effective date of this final rule, manufacturers will not be allowed to import powdered medical gloves. However, while powdered medical gloves will be banned in the United States on the effective date of this final rule, manufacturers may export existing inventory of powdered gloves to a foreign country if the device complies with the laws of that country and has valid marketing authorization by the appropriate authority, as described in section 802 of the FD&C Act (21 U.S.C. 382)). If eligible for export under section 802 of the FD&C Act, a device intended for export will not be deemed adulterated or misbranded if it

(A) accords to the specifications of the foreign purchaser,

(B) is not in conflict with the laws of the country to which it is intended for export,

(C) is labeled on the outside of the shipping package that it is intended for export, and

(D) is not sold or offered for sale in domestic commerce.

V. Effective Date

This rule is effective January 18, 2017. The effective date of this rule applies to devices already in commercial distribution and those already sold to the ultimate user, as well as to devices that would be sold or distributed in the future. All powdered surgeon's gloves, powdered patient examination gloves, and absorbable powder for lubricating a surgeon's gloves must be removed from the market upon the effective date of this final rule. Section 501(g) of the FD&C Act (21 U.S.C. 351(g)) deems a device to be adulterated if it is a banned device.

VI. Economic Analysis of Impacts

A. Introduction

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety,

and other advantages; distributive impacts; and equity). We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the final rule. We believe that this final rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this rule imposes no new burdens, we certify that the final rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before issuing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year.'' The current threshold after adjustment for inflation is $146 million, using the most current (2015) Implicit Price Deflator for the Gross Domestic Product. This final rule would not result in an expenditure in any year that meets or exceeds this amount.

B. Summary of Costs and Benefits

The final rule prohibits marketing of powdered surgeon's gloves, powdered patient examination gloves, and absorbable powder for lubricating surgeon's gloves. The rule does not cover or include powdered radiographic gloves.

The final rule is expected to provide a positive net benefit (estimated benefits minus estimated costs) to society. Banning powdered glove products is not expected to impose any costs to society. Extensive searches of glove distributor pricing indicate that improvements to non-powdered gloves have made these products as affordable as powdered gloves. The ban is expected to reduce the adverse events associated with using powdered gloves. The Agency estimates maximum total annual net benefits to range between $26.8 million and $31.8 million. The present discounted value of the estimated benefits over 10 years ranges from $228.9 million to $270.8 million at a 3 percent discount rate and from $188.5 million to $223 million at a 7 percent discount rate.

FDA has examined the economic implications of the rule as required by the Regulatory Flexibility Act. If a rule will have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires us to analyze regulatory options that would lessen the economic effect of the rule on small entities. This rule will not impose any new burdens on small entities, and thus will not impose a significant economic impact on a substantial number of small entities.

The full discussion of the economic impacts of the rule, which includes a list of changes made in the final regulatory impact analysis, in accordance with Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act, and the Unfunded Mandates Reform Act is available at *https://www.regulations.gov* under the docket number (FDA–2015–N–5017) for this rule and at *http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm#* (Ref. 23).

VII. Analysis of Environmental Impact

FDA has carefully considered the potential environmental effects of this final rule and of possible alternative actions. In doing so, the Agency focused on the environmental impacts of its action as a result of disposal of unused powdered surgeon's gloves, powdered patient examination gloves, and absorbable powder for lubricating a surgeon's glove that will need to be handled after the rule is finalized.

The environmental assessment (EA) considered each of the alternatives in terms of the need to provide maximum reasonable protection of human health without resulting in a significant impact on the environment. The EA considered environmental impacts related to landfill and incineration of solid waste at municipal solid waste (MSW) facilities nationwide. The selected action, if finalized, will result in an initial batch disposal of unused powdered surgeon's gloves, powdered patient examination gloves, and absorbable powder for lubricating a surgeon's glove from user facilities to MSW facilities nationwide, followed by a rapid decrease in the rate of disposal of these devices, as supplies are depleted. The selected action does not change the ultimate disposition of these devices but expedites their rate of disposal and ceases future production. Overall, given the limited number of powdered surgeon's gloves, powdered patient examination gloves, and absorbable powder for lubricating a surgeon's glove, currently in commercial distribution, the selected action is expected to have no significant impact on MSW and landfill facilities and the environment in affected communities.

The Agency has carefully considered the potential environmental effects of this action. FDA has concluded that the action will not have a significant impact on the human environment, and that an environmental impact statement is not required. The Agency's finding of no significant impact and the evidence supporting that finding, contained in an EA, may be seen in the Division of Dockets Management (see **ADDRESSES**) between 9 a.m. and 4 p.m., Monday through Friday (Ref. 24).

VIII. Paperwork Reduction Act of 1995

This final rule contains no collection of information. Therefore, FDA is not required to seek clearance by Office of Management and Budget under the Paperwork Reduction Act of 1995.

IX. Federalism

We have analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

X. References

The following references are on display in the Division of Dockets Management (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at *https://www.regulations.gov*. FDA has verified the Web site addresses, as of the date this document publishes in the **Federal Register,** but Web sites are subject to change over time.

1. ''Guidance for Industry and FDA Staff: Medical Glove Guidance Manual,'' January 22, 2008, available at: *http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM428191.pdf*.
2. ''ASTM D6124 Standard Test Method for Residual Powder on Medical Gloves,'' 2011, available at: *http://www.astm.org/Standards/D6124.htm*.
3. Cote, S.J., M.D. Fisher, J.N. Kheir, et al., ''Ease of donning commercially available latex examination gloves,'' *Journal of Biomedical Matererials Research,* 43(3):331–337, 1998, available at: *http://*

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List of Subjects

21 CFR Parts 878 and 880

Medical devices.

21 CFR Part 895

Administrative practice and procedure, Labeling, Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 878, 880, and 895 are amended as follows:

PART 878—GENERAL AND PLASTIC SURGERY DEVICES

■ 1. The authority citation for part 878 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 360l, 371.

■ 2. Amend § 878.4460 by revising the section heading and paragraph (a) to read as follows:

§ 878.4460 Non-powdered surgeon's glove.

(a) *Identification.* A non-powdered surgeon's glove is a device intended to be worn on the hands of operating room personnel to protect a surgical wound from contamination. A non-powdered surgeon's glove does not incorporate powder for purposes other than manufacturing. The final finished glove includes only residual powder from manufacturing.

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§ 878.4480 [Removed]

■ 3. Remove § 878.4480.

PART 880—GENERAL HOSPITAL AND PERSONAL USE DEVICES

■ 4. The authority citation for part 880 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

■ 5. Amend § 880.6250 by revising the section heading and paragraph (a) to read as follows:

§ 880.6250 Non-powdered patient examination glove.

(a) *Identification.* A non-powdered patient examination glove is a disposable device intended for medical purposes that is worn on the examiner's hand or finger to prevent contamination between patient and examiner. A non-powdered patient examination glove does not incorporate powder for purposes other than manufacturing. The final finished glove includes only residual powder from manufacturing.

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PART 895—BANNED DEVICES

■ 6. The authority citation for part 895 continues to read as follows:

Authority: 21 U.S.C. 352, 360f, 360h, 360i, 371.

■ 7. Add § 895.102 to read as follows:

§ 895.102 Powdered surgeon's glove.

(a) *Identification.* A powdered surgeon's glove is a device intended to be worn on the hands of operating room personnel to protect a surgical wound from contamination. A powdered surgeon's glove incorporates powder for purposes other than manufacturing.

(b) [Reserved]

■ 8. Add § 895.103 to read as follows:

§ 895.103 Powdered patient examination glove.

(a) *Identification.* A powdered patient examination glove is a disposable device intended for medical purposes that is worn on the examiner's hand or finger to prevent contamination between patient and examiner. A powdered patient examination glove incorporates powder for purposes other than manufacturing.

(b) [Reserved]

■ 9. Add § 895.104 to read as follows:

§ 895.104 Absorbable powder for lubricating a surgeon's glove.

Absorbable powder for lubricating a surgeon's glove is a powder made from cornstarch that meets the specifications for absorbable powder in the United States Pharmacopeia (U.S.P.) and that is intended to be used to lubricate the surgeon's hand before putting on a surgeon's glove. The device is absorbable through biological degradation.

Dated: December 13, 2016.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2016–30382 Filed 12–16–16; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 880

[Docket No. FDA–2015–N–0701]

General Hospital and Personal Use Devices: Renaming of Pediatric Hospital Bed Classification and Designation of Special Controls for Pediatric Medical Crib; Classification of Medical Bassinet

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule to rename pediatric hospital beds as pediatric medical cribs and establish special controls for these devices. FDA is also establishing a separate classification regulation for medical bassinets, previously under the pediatric hospital bed classification regulation, as a class II (special controls) device. In addition, this rule continues to allow both devices to be exempt from premarket notification and use of the device in traditional health care settings and permits prescription use of pediatric medical cribs and bassinets outside of traditional health care settings.

DATES: This order is effective on January 18, 2017.

FOR FURTHER INFORMATION CONTACT: Michael J. Ryan, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 1615, Silver Spring, MD 20993–0002, 301–796–6283.

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Executive Summary

A. Purpose and Coverage of the Final Rule

Pediatric medical cribs that meet the definition of a device in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 321(h)) (referred to as pediatric medical cribs or cribs intended for medical purposes) (product code FMS) are regulated by FDA and will have to comply with the special controls identified in this rule for pediatric medical cribs. Cribs that do not meet the device definition (referred to as cribs for non-medical purposes) must meet the Consumer Product Safety Commission's (CPSC's) regulations and guidelines.

In the **Federal Register** of December 28, 2010 (75 FR 81766), the CPSC issued a final rule prohibiting the use of the drop-side rail design for non-medical cribs in consumer households as of June 28, 2011. CPSC's rule established new standards for full-size and non-full-size cribs intended for non-medical purposes, which effectively prohibited the manufacture or sale of cribs intended for non-medical purposes with a drop-side rail design in households, child care facilities, family child care homes, and places of public accommodation. This rule did not affect pediatric medical cribs regulated by FDA, which typically contain a drop-side rail design that includes movable and latchable side and end rails. Although drop-side cribs intended for non-medical purposes are now prohibited, there is still a need for pediatric medical cribs with drop-side rails inside and outside of traditional health care settings. Pediatric medical cribs with drop-side rails are extremely helpful for patient care in hospital settings and even outside of traditional health care settings, such as day care centers caring for infants and children with disabilities, because they allow parents and care givers easy access to children to perform routine and emergency medical procedures, including, but not limited to, cardiopulmonary resuscitation (CPR), blood collection, intravenous (IV) insertion, respiratory care, and skin care. These drop-side rail cribs also make it easier for hospital staff to facilitate safe patient transport and reduce the chance of care giver injury.

Over the last 5 years, FDA has received over 500 adverse event reports, or Medical Device Reports (MDRs), associated with open pediatric medical cribs, through the Agency's Manufacturer and User Facility Device Experience (MAUDE) database. There were adverse event reports of serious injuries, including reports of entrapment, which were predominantly entrapments of extremities (legs or arms). The majority of MDRs for medical cribs were for malfunctions such as drop-side rails not latching or lowering, brakes not holding, wheels or casters breaking, and where applicable, scales not reading correct weights. As a result of the risks to health and need for continued use of pediatric medical cribs in traditional health care settings and non-traditional settings, FDA is revising the identification for § 880.5140 (21 CFR 880.5140) to include only pediatric